UNIVERSITY OF LONDON THESIS

Degree PHD Year 2008 Name of Author BORG-LONGHURST, EUGENIA, ANNE.

Social, psychological and functional outcomes after meningococcal disease in adolescents: A longitudinal population-based case-control study

Thesis presented for the degree of
Doctor of Philosophy
University of London

Eugenia Borg-Longhurst
University College London

2007

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Declaration

I, Eugenia Borg-Longhurst, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Eugenia Borg-Longhurst

Abstract

Meningococcal disease (MD) remains a major source of mortality and morbidity in adolescence despite the introduction in some countries of the seroGroup C conjugate vaccine. This study is the first which comprehensively assesses the outcomes of MD in adolescence. In pursuing this aim, a population-based matched cohort study was undertaken and 101 sex and age matched case-control pairs (aged 15-19 years at disease) from 6 regions of England (representing 65% of the population of England) were followed up 18-36 months after MD (46% males). Educational, social and vocational function, mental health, social support, cognitive and quality of life data were collected using standardised questionnaires and neuropsychological tests. In addition, demographic and disease factors associated with outcome were also examined.

The results show that 57% (N=58) of cases had physical sequelae ranging from minor scarring to bilateral amputations. Survivors had greater mental fatigue, lower social support, greater reduction in quality of life, and lower educational attainment compared with controls. Cognitive testing revealed no overall change in intellectual ability; however, cases had deficits in aspects of memory (short and long-term), attention (selective and sustained), cognitive flexibility and psychomotor speed. Greater cognitive deficit was associated with a younger age at diagnosis. Cases with SeroGroup C disease had greater physical sequelae than those with B disease. MD status increased the risk of depression. Only 53/101 cases reported any medical follow-up after MD.

The findings suggest that survivors of MD in adolescence have a disturbing series of deficits including poorer physical and mental health, quality of life and educational achievement. SeroGroup C is associated with poorer outcome. Of concern, medical care is poor after discharge from hospital. Routine follow up of adolescent survivors is essential to address issues and concerns that are important for adolescent MD survivors and to mitigate or prevent physical and psychosocial morbidity after MD.

Contents

List of Tables

Chapter 4 (continued)

Chapter 5

Chapter 5 (continued)

SECTION D

Chapter 6

List of Figures

List of Abbreviations

A-FILE	Adolescent-Family Inventory of Life Events
ANCOVA	Analyses of Covariance
ASBIR	Annotated Scale of Bodily Injuries Regulation
BCG	Bacillus Calmette-Guerin vaccine
BDI-II	Beck Depression Inventory – Second Edition
CANTAB	Cambridge Neuropsychological Test Automated Battery
CSF	Cerebral Spinal Fluid
CORE-OM	Clinical Outcome Research Evaluation Outcome Measure
CSS	Cognitive Summary Score
CI	Confidence Interval
DMS	Delayed Matching to Sample test
DNA	Deoxyribose Nucleic Acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
FMS	Fulminant Meningococcal Septicaemia
GBS	Group B Streptococcal
Hib	*Haemophilus Influenzae* type b
HPA	Health Protection Agency
HPA CDSC	Health Protection Agency Communicable Disease Surveillance Centre
HRQoL	Health Related Quality of Life
ICU	Intensive Care Unit
ICP	Intra Cranial Pressure
IED	Intra-Extra Dimensional Set Shift
MTS	Matching to Sample
MD	Meningococcal Disease
MM	Meningococcal Meningitis
MRU	Meningococcal Reference Unit
MS	Meningococcal Septicaemia
MCS	Mental Health Component Summary Score
NART	National Adult Reading Test
OR	Odds Ratio
OMPs	Outer Membrane Proteins
PICU	Paediatric Intensive Care Unit
PAL	Paired Associate Learning
PCS	Physical Component Summary Score

List of Abbreviations (continued)

PCR	Polymerase Chain Reaction
PTSD	Post Traumatic Stress Disorder
QOL	Quality of Life
RVP	Rapid Visual Processing test
RT	The Five Stage Reaction Time task
RAVLT	Rey Auditory Verbal Learning Test
ROCF	Rey-Osterrieth Complex Figure Test
RNA	Ribose Nucleic Acid
SES	Socioeconomic Status
SSQ6	Sarason Social Support Questionnaire
SF36-II	Short Form 36 Health Survey Version II
SRM & PRM	Spatial & Pattern Recognition Memory
SSP	Spatial Span Test
SWM	Spatial Working Memory
SD	Standard Deviation
SHP	Stated Handed Preference Questionnaire
SOC	Stockings of Cambridge
WAIS-R	Wechsler Adult Intelligence Scale – Revised
WBC	White Blood Count
WISC-III	Wechsler Intelligence Scale for Children, 3rd Edition, UK
WISC-R	Wechsler Intelligence Scale for Children – Revised

Acknowledgements

The study on which I report would not have been possible without the willing participation of the young people and their families to whom I would like to extend my gratitude and appreciation.

My sincere thanks are addressed to my supervisors Dr Russell Viner, Dr Deborah Christie and Professor Robert Booy who provided the rationale and basis of this work, and the best support I could have desired. I would like to thank them for the opportunity, the motivation, the encouragement, and the generosity in their supervision. I could not have hoped for better role models. All three have contributed to my personal and professional development.

I would also to thank Professor Peter Hindmarsh for his support as an additional supervisor from University College London.

The Meningitis Research Foundation, to whom I am indebted, funded the research study, which forms the basis of my thesis.

Finally, I want to thank my husband Alexander for his unconditional encouragement, and whose continued support sustained me throughout the course of my studies.

Structure of dissertation

This thesis comprises five sections.

Section A (Background) comprises two chapters. Chapter 1 provides an overview of Meningococcal Disease (MD), and in particular, describes the microbiological characteristics of *Neisseria meningitides*, the transmission and pathogenesis of meningococci, and outlines the risk factors associated with the disease. The chapter further discusses the pathophysiology of the disease, and the epidemiology of MD. Chapter 2 reviews the outcomes of MD and in particular focuses on the design of outcome investigations with reference to the effects of MD in adolescence.

Section B (Methods) comprises Chapter 3 and deals with the aims of the study, its design characteristics, and the outcomes measured. It further provides a summary of the aims of both the cross-sectional and longitudinal analyses undertaken by the study.

Section C (Results) consists of Chapters 4 and 5 both of which describe the findings of the study. Chapter 4 deals primarily with the outcomes of the cross-sectional analyses and concludes with summarising the associations of identified deficits on functioning. Chapter 5 discusses the outcomes of the longitudinal analyses and highlights the differences between cases and controls in health behaviours.

Section D (Conclusions) includes Chapters 6 and 7. Chapter 6 focuses on the results of the study under review, provides a discussion of the issues emerging from the evidence obtained and highlights the implications of the results for future practice and further research. The discussion also focuses on the methodology of the study and addresses its strengths and limitations. Chapter 7 provides a conclusion to the thesis drawing on the salient findings of the study and outlines future research directions.

Section E includes the references.

SECTION A

"Few infections can cause the civil, medical, and social stress that occurs when serious meningococcal disease enters a community" (Apicella 1995).

CHAPTER 1 – OVERVIEW OF MENINGOCOCCAL DISEASE

1.1 Introduction and aims

Invasive meningococcal disease (MD) is an infectious and potentially life-threatening systemic infection causing septicaemia and/or meningitis. It is caused by the bacterium *Neisseria meningitidis* and is globally endemic with periodic epidemics in developing and to a lesser extent, developed countries (Jones and Mallard 1993; Ramsay *et al.* 1997). It is the most common cause of bacterial meningitis worldwide, with over 500,000 cases reported annually (Hubert and Caugant 1997;Ramsay *et al.* 1997; Tikhomirov *et al.* 1997; World Health Organisation 2002b). Overall mortality in population-based studies including all ages is approximately 7% (Erickson and De Wals 1998). The World Health Organization estimated that MD was the cause of 171,000 deaths worldwide in 2000 (WHO 2005).

While the primary incidence peak for MD is in children aged <5 years, there is a secondary peak in older teenagers and, the case-fatality rate can be up to five times higher among 15-24 year olds compared with other age groups (Harrison *et al.* 2001; Jones and Mallard 1993). The reasons for the peak of MD in teenagers are poorly understood. Greater transmission of meningococci has been implicated, (Coen *et al.* 2000) as prevalence of carriage increases especially through childhood (Cartwright *et al.* 1987).

Throughout the 1990s, the incidence of MD in adolescents and young adults increased in comparison to the general population in the UK, (Jones and Mallard 1993) and in many other European countries (Connolly and Noah 1999), including the United

States (Harrison *et al.* 2001;Rosenstein *et al.* 1999). Despite the introduction of a highly effective conjugated meningococcal C vaccine (Bose *et al.* 2003), high rates of meningococcal disease remains as seroGroup B disease remains a major cause of death and morbidity in adolescents (Ramsay *et al.* 2001;Trotter *et al.* 2002). In 2003-04 there were on average 223 annual cases of invasive MD in 10-19 year olds in England and Wales (Health Protection Agency 2007a).

Significant physical sequelae of MD are believed to occur in 3-15% of cases of all ages in developed countries (Baraff *et al.* 1993; Erickson and De Wals 1998). However, in more recent studies the proportion of survivors with long-term sequelae was estimated at 13% in individuals under the age of 18 years (Stovall and Schutze 2002) and 20% in young adults (Erickson *et al.* 2001).

Adolescents aged 15 years or older appear more likely than infants and children to have the septicaemic form of the disease (Harrison *et al.* 2001), thereby increasing the risk of cognitive impairment, epilepsy, vasculitis arthritis, and sensorineural hearing loss, in addition to the physical sequelae (Baraff *et al.* 1993). Adolescents appear to be at greater risk of scarring, amputations and hearing loss post-MD (Erickson and De Wals 1998). They may also have the highest case-fatality rate of any age group (Harrison *et al.* 2001).

Little is known of the long-term effects of MD in adolescence, or of which factors increase the risk of poor outcomes. Outcome studies have examined MD alongside variant aetiologies of bacterial meningitis in young children and have primarily focused on physical sequelae (Baraff *et al.* 1993; Fellick *et al.* 2001). Results are unlikely to be generalisable to adolescents and young adults.

Vocational, educational, and cognitive outcomes have not been studied in adolescence although there are anecdotal reports that adolescent MD survivors believe that the illness affected their educational success and vocational choices (Sander *et al.* 1984a).

Neurological functions such as concentration, memory and attention remain sensitive to trauma in adolescence (Brown 2000;Tapert and Brown 1999) therefore the impact

of MD may be particularly problematic during adolescent transitions into higher education, adult employment and social relations.

Moreover, there is evidence that during adolescence important structural changes take place in the brain suggesting it is vulnerable to damage (Giedd *et al.* 1999). Septicaemia may cause cerebral insult due to vasculitis and cerebral hypotension, the release of inflammatory factors within the brain, and the occurrence of small septic infarcts. This is more likely to cause damage during the period of development of formal operational thought. However, detailed studies of the outcomes of MD in adolescence have not been published. Moreover, a consistent and specific profile of neuropsychological abnormalities has not been established in adolescent survivors of MD.

Adolescence is traditionally viewed as a time of physical and emotional change, optimal health with low levels of morbidity, and is typified by attempts to establish autonomy and independence, close personal relationships and define work goals (Erickson 1959). Attainment of all these goals is fundamental to a successful passage through adolescence: life-threatening illnesses such as MD can potentially compromise these achievements. Clarifying the extent of complications in teenage survivors is critical to the development of relevant interventions to aid recovery and improve quality of life in the years that follow such a life threatening illness.

This thesis describes a prospective matched cohort study undertaken to examine the hypotheses that survivors of MD in adolescence have poorer educational, vocational, social and psychological function, quality of life and cognitive function than matched controls. In addition, that poorer outcome is seen in those with seroGroup C disease whether meningitis septicaemia or mixed. Whether medical follow-up was achieved was also examined in survivors and its impact on outcome was assessed.

The following provides an overview of the historical background of MD, the transmission and pathogenesis and the risk factors associated with the disease. The chapter further discusses the pathophysiology and the epidemiology of MD to inform discussion on outcomes.

1.2 Historical summary

Descriptions of illness resembling meningococcal disease (MD) have been reported throughout history (Willis 1684). However, it was not until 1806 that Vieusseux reported the first clear account of an outbreak of MD during an epidemic of spinal meningitis in Eaux Vives on the outskirts of Geneva, Switzerland. This was the first well-documented description of an outbreak of MD. It resulted in 33 deaths (Vieusseux 1806). In the same year and independent of Vieusseux, a description of an outbreak of MD was reported from New England, USA (Danielson and Mann 1806). This was the first report of the disease in the New World.

In 1884 the Italian pathologists Marchiafava and Angelo Celli first described intracellular oval micrococci within leucocytes in the samples of Cerebral Spinal Fluid (CSF) from patients dying with meningits (Marchiafava and Celli 1884).

Further outbreaks of MD were comprehensively documented by, Hirsch, a medical historian, in Europe, Africa, Asia and the Americas. These occurred throughout the 19th century and he described principal epidemic periods of "cerebro-spinal meningitis" with very high case fatality rates (Hirsch 1886).

A breakthrough came in 1887 when Anton Weichselbaum, a Viennese pathologist and bacteriologist, first identified the bacterium causing MD in the CSF of six of eight patients of primary, sporadic meningitis when a coccoid bacterium was isolated from meningeal exudates (Weichselbaum 1887). This was the first isolation of a meningococcus. The organism was then called *Diplococcus intracellularis meningitidis*, which became known as *Neisseria meningitidis* after the German scientist and clinician, Albert Neisser who discovered the Neisseria group of bacteria.

Asymptomatic carriage was identified in 1896 in Europe (Kiefer 1896) and was linked with the incidence of MD some years later (Bruns and Hohn 1908).

Despite the numerous historical milestones in understanding MD, invasive infection continues to be a serious and life-threatening disease and in 1919 Herrick stated: "no other infection so quickly slays"(Herrick 1919). Nearly 90 years later, this still holds

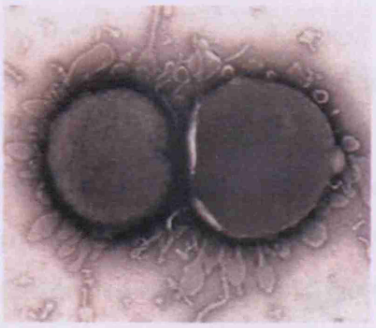
true as it remains the commonest cause of bacterial meningitis worldwide (Hubert and Caugant 1997;Ramsay *et al.* 1997; Tikhomirov *et al.* 1997;World Health Organisation 2002a).

1.3 Microbiological characteristics

Neisseria meningitidis, also known as the meningococcus is an aerobic, bean-shaped gram-negative, bacterium that occurs in pairs (diplococci) and can be encapsulated or unencapsulated (Stephens *et al.* 2007a). See Figure 1.1. It is related to several nonpathogenic *Neisseria* species, such as *N. lactamica*. MD is the collective name for the pathological syndromes caused by *N. meningitidis* (Stollenwerk *et al.* 2004).

The meningococcus is highly pathogenic and virulent and exclusively a human pathogen. It is also very fragile as it does not survive well outside the human host and needs certain growth conditions for it to multiply. Meningococci can infect diverse sites within the human host, although primarily they infect the upper respiratory tract, as they need a fairly solid yet moist basis to grow. Invasive strains produce a polysaccharide capsule, whereas strains carried asymptomatically are often acapsular (Yazdankhah and Caugant 2004).

Figure 1.1 – Electron microscopy of a pair of meningococci



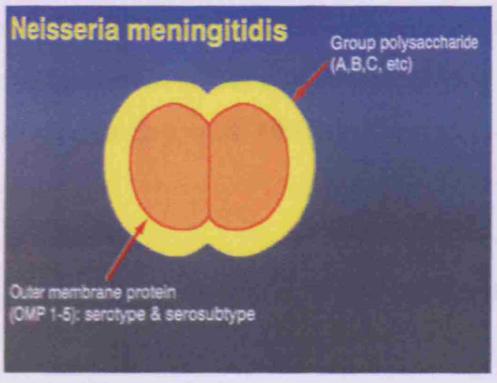
Source: Meningitis UK

The meningococcus has an inner (cytoplasmic) membrane containing water, salts, deoxyribose nucleic acid (DNA), ribose nucleic acid (RNA), various structures (e.g. ribosomes), proteins, enzymes, and other substances necessary for life (Vogel and

Frosch 1999). It also has an outer membrane separated from the inner membrane by a cell wall. The outer membrane contains protein structures and toxic lipopolysaccharides (or endotoxin), that enable the bacteria to interact with the host cells as well as perform other functions. It is surrounded by an antiphagocytic polysaccharide capsule, which is important in the pathogenesis of MD. There are five different protein structural classes within outer membrane proteins (OMPs), which link together to form a mesh, giving the bacterium its shape. There is also a thin layer of peptidoglycan in the periplasmic space (Morley and Pollard 2001).

Meningococci are classified by using serologic methods and come in many different forms with different strains classified based on their antigenically and chemically distinct capsular structure (Rosenstein *et al.* 2001). They are divided into various subgroups; called seroGroups (see Figure 1.2).

Figure 1.2



Source: Meningitis Trust

At least 13 different seroGroups of meningococci have been thus far identified namely, A, B, C, D, E29, H, I, K, L, W135, X, Y and Z. They can be further subdivided and classified based on identification of the different types of outer membrane proteins (OMPs): 20 serotypes, 10 serosubtypes, and 13 immunotypes designated by the letter L have been identified (Pollard and Levin 2000;van Deuren *et al.* 2000). Chromosomal DNA (genotype) also differentiates the bacteria.

An example of the standard classification on type of meningococci (each separated by a colon) is B: 4: P1.4, denoting seroGroup B, serotype 4, and serosubtype P1.4 (van

Deuren *et al.* 2000). Knowledge of the exact capsular and genetic structure of a strain is essential to the development of treatments, especially vaccination strategies. An individual, genetically unique bacterium is known as a strain, which essentially clones itself in the course of a disease in order to spread.

Meningococci are genetically diverse with only a small subset of genotypes associated with invasive disease (van Deuren *et al.* 2000).

Most cases of invasive disease worldwide are caused by seroGroups A, B, C, Y and to a lesser extent, W135 (Pollard and Levin 2000) and more recently seroGroup X has emerged (Rosenstein *et al.* 2001; Stephens 2007b). SeroGroups B and C are responsible for the overwhelming majority of cases in the United Kingdom (Health Protection Agency 2007b)

Meningococci have the ability to exchange genetic material and so can switch serogroups: under immune pressure a 'capsule switch' may occur, changing for example from seroGroup B to C or vice versa in order to survive (Caugant 1998;Swartley *et al.* 1997).

1.4 Transmission and pathogenesis

1.4.1 Transmission

Transmission of meningococci, may be person to person by direct close contact or by aerosol droplets from the upper respiratory tract through coughing, sneezing or via the spread of saliva from someone who is carrying the organism (Cartwright 1995b), leading to colonisation or carriage (Stephens *et al.* 2007b). It has been proposed that some climatological conditions for example, temperature and humidity, can enable meningococci to survive in respiratory droplets (van Deuren *et al.* 2000). Close contacts include household members, and anyone who has been directly exposed to the person's oral or nasal secretions.

Meningococci adhere to the surface of the naso-oropharyngeal mucosal lining of the upper respiratory tract (the principal reservoir), for example, the throat and nose. This is where the bacteria typically reside and to a much lesser extent, the urogenital tract and anal canal. Adherence to the mucosal cells occurs via the pili found in virtually all gram-negative bacteria which are long thin tubular protein protrusions within the meningococcus that extend from the surface to allow for this initial binding (Feigin 1992;Heckels 1989).

1.4.2 Colonisation

The pathophysiologic process of MD commences with colonisation of the upper respiratory tract (Nassif *et al.* 2002). Colonisation or carriage of meningococci may be transient, persist for several weeks or even years, providing an ongoing source of infection for others. The bacteria can flourish without disease ever breaking out and then spontaneously disappears. Carriage is a prerequisite for invasive disease (Goldschneider *et al.* 1969).

Infection in the majority of cases results in asymptomatic carriage rather than invasive disease as serum antibodies attach to the surface of the bacteria: immune responses usually ensure that the bacteria are killed before they can cause disease (Cartwright 1995b). The majority of strains isolated from most adults and children have been found to be non-pathogenic (Bevanger *et al.* 1998;Cartwright *et al.* 1987;Gold *et al.* 1978). In fact, carrier status appears to provide some protection to those who harbour the bacteria in their upper respiratory tracts (Goldschneider *et al.* 1969).

Carriage of meningococci is relatively common and at any one time, meningococci colonise 8-25% of healthy individuals in their nasopharynx in a harmless way (Cartwright 1995b; Stephens 1999), with systemic infection occurring in less than 1% of colonised persons (Aycock and Mueller 1950).

The number of individuals in a population who are "carriers" varies greatly depending on the region of the world, the season and the age of the individuals. Worldwide there is said to be approximately 500 million carriers of the bacterium in their nasopharynx (Almeida-Gonzalez *et al.* 2004).

It is not fully known why some people become ill whilst others are only infected and remain well. This pool of healthy asymptomatic carriers is why the infection spreads. While the events, which enable certain strains of meningococci to pass through the nasopharyngeal membrane into the bloodstream, remain poorly understood, it is clear that survival in the bloodstream, and the ability to multiply to high numbers, are an essential requirement for severe disease to occur. What is known is that damage to the physical integrity of the naso-oropharyngeal ciliated epithelium is fundamental for meningococcal invasiveness (Rayner *et al.* 1995) in order to enable the meningococci to gain access to the bloodstream (Cartwright *et al.* 1987; Mueller *et al.* 2006; Stephens *et al.* 2007a; Yazdankhah and Caugant 2004). Persons newly colonised with meningococci are much more at risk of developing the disease than those with an established colonisation particularly if acquisition with a particularly virulent clone occurs (Edwards *et al.* 1977;Marks *et al.* 1979). Only a small proportion of carried strains are responsible for most cases of invasive disease (Bygraves *et al.* 1999).

A number of factors have been linked to increased carriage rates:

1.4.2.1 Age and gender

Carriage of meningococci is highest among teenagers and young adults aged 15 to 24 years (as high as 24% to 37%) (Cartwright 1995b; Coen *et al.* 2000;Trotter *et al.* 2005) who play an important role in the transmission of virulent strains across the population (Trotter *et al.* 2005). Rates are lowest in children under 5 years of age (2% to 3%), and less than 10% in older age groups (Bevanger *et al.* 1998;Cartwright *et al.* 1987;Caugant *et al.* 1994; Ceesay *et al.* 1993;Public Health Laboratory Service Meningococcus Forum. 2002).

A number of studies have found that more males than females are likely to be carriers (Cartwright *et al.* 1987;Caugant *et al.* 1994; Gilmore *et al.* 1999;Neal *et al.* 2000).

1.4.2.2 Socioeconomic deprivation and overcrowding

Carriage rates have been found to be higher in lower socioeconomic groups (Baker *et al.* 2000; Fontanals *et al.* 1995;Moodley *et al.* 1999;Stanwell-Smith *et al.* 1994) (Krizova and Kriz 1999). This may simply be due to overcrowding as other studies

have found increased carriage in people who are brought together from different places, for example military recruits, pilgrims, boarding school students, or prisoners (Goldschneider *et al.* 1969;Moore *et al.* 1989; Pether *et al.* 1988;Schubiger *et al.* 1986; Tappero *et al.* 1996). This could be one of the reasons why carriage rates are much higher in younger people as they are more likely to move into boarding schools, universities (or at least attend classes for many hours per day) and the armed forces where carriage rates up to 50% have been found (Farrell and Dahl 1966).

1.4.2.3 Social and health risk behaviours

Other factors linked to increased pharyngeal carriage rate are active cigarette smoking and passive exposure to smoke with numerous studies to support this, both in adults and children (Blackwell *et al.* 1992;Blackwell and Weir 1990;Caugant *et al.* 1994;Fischer *et al.* 1997; Haneberg *et al.* 1983; Kremastinou *et al.* 1994;Riordan *et al.* 1998; Simons 2001;Stanwell-Smith *et al.* 1994; Stuart *et al.* 1989a).

It has been suggested that smokers may be more densely colonised by a variety of potentially pathogenic bacteria and also that passive smoking can coat mucosal surfaces of the nasopharynx which enhances the binding of potentially pathogenic bacteria (Haneberg *et al.* 1983)

A large British study (MacLennan *et al.* 2006), examined carriage and social behaviour in 14,000 British teenagers aged 15 to 19 years of age. The young people who were assessed either attended school or college full-time but none were at university. The authors reported that attendance at pubs/clubs, intimate kissing of multiple partners, and active cigarette smoking, increased the risk of meningococcal carriage, as did exposure to passive smoking. However, in contrast to previous studies no association was found between increased carriage and gender, social deprivation, or home crowding. The authors concluded that social behaviour is largely responsible for the increase in meningococcal carriage seen in teenagers and is likely to explain the peak in MD attack rates in teenagers.

Other studies have also found increased carriage rates amongst those who attend night clubs or bars (Caugant *et al.* 1994;Conyn-van Spaendonck *et al.* 1999; Imrey *et al.* 1995;Imrey *et al.* 1996; Neal *et al.* 2000), places often frequented by young people.

Other factors found to increase carriage rates include stress and preceding viral infections (Cartwright *et al.* 1991b; Conyn-van Spaendonck *et al.* 1999;Dominguez *et al.* 2001;Haneberg *et al.* 1983; Raza *et al.* 1999), which may alter the integrity of the mucosal surface of the nasopharynx or influence local or systemic immunity.

Treatments for reducing the nasopharyngeal carriage of *Neisseria meningitidis* involve antibiotics such as rifampin, ciprofloxacin, and ceftriaxone which have been found to be 90%-95% effective (Deal and Sanders 1969; Gaunt and Lambert 1988;Schwartz *et al.* 1988).

1.4.3 Risk factors associated with MD

Why some individuals are susceptible to invasive disease is not clearly understood although a number of risk factors have been implicated and many of the factors that increase carriage of meningococci are also risk factors for invasive disease. This section will explore risk factors for MD, and those associated more specifically with young people.

1.4.3.1 Age and gender

Although MD can affect people at any age certain groups seem to be at increased risk of contracting the disease, for example studies conducted in the USA and the UK have found that males were at a higher risk of contracting MD than females (Abbott *et al.* 1985; Fallon *et al.* 1984;Klein *et al.* 1986). Furthermore, although children < 5 years of age are at the highest risk for getting the disease, rates fall through later childhood and begin to rise again in early adolescence, peaking between the ages of 15 and 19 years indicating that teenagers are particularly vulnerable (Morley and Booy 1997). This may well be due to the social and behavioural changes, which occur in this age group contributing to their susceptibility of MD.

1.4.3.2 Medical conditions

A number of medical conditions have also been found to increase the risk of developing MD. For example, chronic underlying illness has also been found to increase susceptibility to meningococcal infection in older patients (Stephens *et al.* 1995) as well as certain genetic risk factors (Hibberd *et al.* 1999).

Further, infections such as viral (influenza A virus), adenovirus, parainfluenza, rhinovirus, mycoplasma, and respiratory syncytial virus and other upper respiratory tract infections have been found to precede the disease in all ages (Bruce *et al.* 2001;Cartwright *et al.* 1991a; Haneberg *et al.* 1983;Harrison *et al.* 1991;Kriz *et al.* 2000;Levitt *et al.* 1970;Moore *et al.* 1990;Robinson *et al.* 2001; Tully *et al.* 2006;Watson *et al.* 1996;Young *et al.* 1972). Infection with Epstein-Barr virus has also been implicated in increase risk of MD (Evans and Niederman 1998).

A recent study investigating the risk and protective factors in a large sample [144 case control pairs] of adolescents (aged 15-19 years) found that preceding upper respiratory infection was an important risk factor for MD in this age group (Tully *et al.* 2006).

Other studies have pointed to rare immune defects as increasing susceptibility to pathogenic and non-pathogenic strains of *N. meningitidis* but these only represent a small proportion of the overall number of cases (Hoare 1999; Rosenstein *et al.* 2001;Schwartz *et al.* 1989; Stephens 1999; World Health Organisation 2002a). For example, complement deficiencies (Ellison *et al.* 1983), functional or anatomical asplenia (as in the case of patients with sickle cell disease) (Figueroa and Densen 1991; Franke and Neu 1981) and persons with immature or dysfunctional humoral immunity (Goldschneider *et al.* 1969) were found to increase susceptibility to MD.

1.4.3.3 Lifestyle and environmental factors

Certain lifestyle and environmental factors characteristically of adolescents and young adults pose an increased risk for acquiring the disease These include residential accommodation with young people from geographically diverse areas (i.e. schools, colleges, university halls of residence or military barracks), which are places where the opportunity for spread is increased (Fischer *et al.* 1997; Harrison *et al.* 2001).

Studies on university students residing on campus are clear examples of the influence of crowded living conditions increasing the risk of meningococcal infection (Bruce *et al.* 2001;Jackson *et al.* 1995). Outbreaks in UK university students in recent years have drawn attention to the risk in this group with large numbers of cases reported for example, at Cardiff University (Anonymous 1996) and in November 1996 and

October 1997 at the University of Southampton (Anonymous 1997), involving a total of 13 cases in students, 5 of whom died. It is unclear why particular halls of residence should have a greater risk of cases or clusters of disease than others. Although students tend to share beverages or utensils, go to bars, actively or passively smoke and practice irregular sleeping patterns, precise mechanisms are unclear.

In the large population-based study examining risk and protective factors in 15-19 year old survivors (Tully *et al.* 2006), university and school students were found to be at higher risk of MD than people in employment. But contrary to the above studies the authors did not find that living in dormitory-style accommodation increased risk, however numbers were small (7% of cases, 6% of controls).

Overcrowding has been a known risk factor since World War I, where it was found to increase susceptibility of MD amongst military recruits (Blackwell *et al.* 1992; Hirsch 1886;Riordan *et al.* 1998). Prison inmates experiencing crowding may also be at increased risk (Thomas *et al.* 1991). In military camps, large numbers of young adult males (a group with a high meningococcal carriage rate) are brought into close proximity for periods of several months, this favours enhanced transmission of meningococci.

The incidence of disease is higher in the winter in for example, Europe and North America, which may be due to crowding of people in poorly ventilated houses, where spread of virulent meningococci is enhanced. In addition, close proximity to a person diagnosed with disease (e.g., being a household contact) significantly increases the risk of developing disease (DeWals *et al.* 1981;Meningococcal Disease Surveillance Group 1974).

Interestingly, in a study examining risk and protective factors in 15-19 year old MD survivors (Tully *et al.* 2006), religious observance was associated with protection from MD, which has been supported by other studies (Fischer *et al.* 1997). Religious observance has been found to have beneficial immune effects (Koenig *et al.* 1997). Attendance at religious event may be associated with other lifestyle factors that promote health and protect against infection (McCullough *et al.* 2000).

1.4.3.4 Health risk behaviours

Several health behaviours in adolescents have been demonstrated to increase the risk of infection for example, intimate kissing with multiple partners, was significant in the study examining the risk and protective factors for MD (Tully *et al.* 2006). Kissing on the mouth has been suggested to be a risk factor in children (Stanwell-Smith *et al.* 1994), although no evidence supporting this was found in adolescents in the same study.

Smoking has been described as being responsible for as much as almost one third of all cases of MD (Rosenstein *et al.* 2001). Smoking marijuana has also been linked to a number of cases of MD in the USA (Krause *et al.* 2001). Contact with smokers has been found to be associated with increased risk of MD in adolescents (Coen *et al.* 2006).

In children aged less than 5 years, passive smoking in the home (30 or more cigarettes daily) was found to be associated with MD (Stanwell-Smith *et al.* 1994). Other studies have also found that passive smoking increases the carriage rate (Haneberg *et al.* 1983;Robinson *et al.* 2001;Stuart *et al.* 1988;Stuart *et al.* 1989). This may be due to smoke interfering with ciliary action, increasing mucus production and decreasing macrophage production, thereby decreasing the body's local defence against potential pathogens (Crofton and Douglas 1981).

In contrast, other studies in adolescents and young adults found no significant role for active or passive smoking (Bruce *et al.* 2001;Nelson *et al.* 2001;Tully *et al.* 2006).

Other factors linked to increased risk of MD include social deprivation (Cartwright 1995b; Foster *et al.* 1971;Jones *et al.* 1997;Stuart *et al.* 1988), stress from certain life events; relationship problems, and legal disputes (Stanwell-Smith *et al.* 1994). Climate and damp living conditions have also all been associated with increased risk (Haneberg *et al.* 1983; Stanwell-Smith *et al.* 1994; Stuart *et al.* 1988;Young *et al.* 1972).

1.5 Pathophysiology

1.5.1 Development of MD

Invasive MD only occurs only when there is exposure to and colonisation with a virulent strain, and invasion of the meningococcus in the bloodstream (van Deuren *et al.* 2000). These processes are influenced by the characteristics of the strain of meningococci, (e.g. the virulence), environmental factors (for example, climate and social conditions) and lastly host factors, for example the immune status of the patient (Achtman 1995). The incubation period is 2-10 days, but usually three to five days (Boutet *et al.* 2001) with signs and symptoms developing over this period.

Once the meningococcus has reached the bloodstream a wide range of clinical syndromes can result, but most commonly meningitis and / or septicaemia (meningococcaemia) (Edwards and Baker 1981;Kirsch *et al.* 1996). Less frequently, infection causes pneumonia, septic arthritis, conjunctivitis, and pericarditis.

1.5.2 Diagnosis

Laboratory confirmation of MD is important for the identification and management of cases and outbreaks, as well as for regional and national surveillance and detection of epidemiologic trends over time. Confirmation requires bacteriological isolation of *N. meningitidis* bacteria from a sterile site, such as blood or cerebrospinal fluid (CSF), or synovial, pericardial, and pleural fluid. Skin scrapings may also yield positive microscopy of culture from a petechial or purpuric lesion. However, in patients with meningococcal meningitis, skin lesions infrequently reveal meningococci with CSF offering the best chance of yielding an organism for culture (Frieling *et al.* 1996). Because lumbar puncture is not advisable in patients with circulatory compromise or any evidence of raised Intra Cranial Pressure (ICP) (Nadel 2001) early diagnosis is not always possible.

Polymerase chain reaction (PCR) testing to identify the capsular serogroup by meningococcal DNA in blood or CSF has been shown to be a reliable tool for rapid diagnosis and as such has become the gold standard for specific diagnosis of MD

(Carrol *et al.* 2000). Indeed one study demonstrated that performing PCR assays of blood or CSF in probable cases of MD can contribute significantly to case ascertainment (Carrol *et al.* 2000). PCR tests have been used widely in the UK since late 1996 (Rosenstein *et al.* 2001). Subtyping of the invasive strain may also be indicated when clusters of cases occur to determine whether they are caused by a single strain.

Rapid administration of antibiotics is recommended when the diagnosis of MD is suspected which is good practice for the patient although it may prevent laboratory diagnosis. Antibiotics can potentially alter the Gram staining characteristics of the organism as the meningococcus is extremely sensitive (Wylie *et al.* 1997). Lack of a definitive diagnosis may underestimate the true burden of disease in the population. As a result blood cultures or CSF are reported to be rarely positive after antibiotic treatment (Baines and Hart 2003), although others report that meningococcal DNA can be found in the CSF up to 96 hours after commencing antibiotics (Ragunathan *et al.* 2000). Furthermore, prior antibiotic administration has been shown not to jeopardise skin biopsy specimens (Frieling *et al.* 1996).

In England and Wales meningococcal septicaemia and meningococcal meningitis are statutorily notifiable diseases under the Public Health (Infectious Disease) regulation 1988 (HMSO 1988) and under Scottish legislation as meningococcal infection. Clinicians are required to notify suspected cases to the regional consultant in communicable disease control or the consultant in public health medicine. Information is then collected on individual patient factors and sent to the regional and national epidemiology centres where it is further integrated with laboratory results (Health Protection Agency Meningococcus Forum 2006).

1.5.3 Clinical Presentation of Invasive MD

Clinical syndromes caused by *N. meningitidis* include meningitis, with or without septicaemia, relatively mild bacteraemia, fulminant meningococcemia, meningoencephaltis, pneumonia, septic arthritis, as well as other presentations (Apicella 2000). Most commonly meningococcal infection presents as meningococcal

meningitis (MM) occurring in about 60% of patients or meningococcal septicaemia (MS), also known as meningococcaemia, presenting in approximately 5 to 20% of patients (Edwards and Baker 1981; Kirsch *et al.* 1996;Rosenstein *et al.* 1999). Mixed presentation of septicaemia and meningitis occurs in approximately 10% of cases (Brandtzaeg 2006).

Adolescents 15 years or older are more likely than infants and children to have the septicaemic form of the disease (40% vs. 20% respectively) and as a result they are at greater risk of a fatal outcome (22.5% vs. 4.6% respectively) (Harrison *et al.* 2001). Overall, case fatality rates of MD have remained stable over the last 20 years, at 9 to 12 %, with a rate of up to 40% among patients with meningococcal septicaemia (Rosenstein and Perkins 2000).

Early symptoms of MD are usually vague and are rarely classical. As a result the disease is often misdiagnosed as something less serious such as influenza or an upper respiratory tract infection (Apicella 2000; Dashefsky *et al.* 1983;Gedde-Dahl *et al.* 1990;Shapiro *et al.* 1986;Sullivan and LaScolea, Jr. 1987). This presents a difficult task for the General Practitioner (GP) who is often the first person a patient sees and who has the difficult task of differentiating the symptoms of MD from what appears to be a less serious illness.

However, symptoms can progress very rapidly and vary according to the number of bacteria present, the organs that have become infected, whether septicaemia occurred, the strain of the disease, as well as other contributing factors.
A number of host and clinical factors have been implicated in the outcome of MD. For example, numerous studies have found age to be a factor with a fatal outcome reported to be highest in infants, adolescents and patients >50 years of age (Anderson 1978;Fallon *et al.* 1984;Halstensen *et al.* 1987;Harrison *et al.* 2001; Riordan *et al.* 1995;Scholten *et al.* 1994;Spanjaard *et al.* 1987;Thomson *et al.* 1991).

The clinical presentation of MD has also been shown to affect outcome with case fatality rates highest in patients presenting with septicaemia compared to mixed disease or meningitis alone (Anderson 1978;Barquet *et al.* 1999; Riordan *et al.* 1995;Thomson *et al.* 1991). Clinical features found to predict poor prognosis include

the presence of shock, the absence of meningism, rapidly progressive purpuric rash, low peripheral white blood cell count, thrombocytopenia, and a depressed conscious level (Nadel *et al.* 1995;Stiehm and Damrosch 1966). Features found to predict permanent and disabling sequelae post MD include focal neurologic signs and haemorrhagic diathesis (Barquet *et al.* 1999).

1.5.3.1 Meningococcal meningitis

Meningococcal meningitis (MM) is predominately a central nervous system infection and is fatal in up to 10% of cases (Kirsch *et al.* 1996). However, with appropriate antibiotics and good clinical surveillance, the mortality rate can be as low as 1 to 2% (van Deuren *et al.* 2000).

Wide presentations can occur in all ages and in the early stages is often non-specific and not associated with petechiae (Thomson and Riordan 2000). Patients may present with sudden onset of fever, headache, meningism and signs of cerebral dysfunction but usually it develops over several days (Thomson and Riordan 2000). Other symptoms include nausea and vomiting, which are often accompanied by photophobia. In some patients, seizures often accompany these symptoms. After the disease has taken hold, a rash may appear. Although typical of septicaemia, the rash can appear in both meningitis (including pure meningitis) and septicaemia (Cartwright 1995b). The meningococcal rash is non-blanching, that is it does not fade under pressure.

Infants and the elderly may not present with the classic symptoms and signs of MM (Tunkel and Dolin 2000) with meningism absent in neonates and also absent often in infants (Saez-Llorens and McCracken 1990).

Patients with meningitis usually have a low concentration of meningococci and endotoxin in plasma but higher concentrations and build up in the cerebral spinal fluid (CSF), (Brandtzaeg *et al.* 1989a; Brandtzaeg *et al.* 1992;van Deuren *et al.* 1995), leading to overt meningitis within 24 to 36 hours (Brandtzaeg *et al.* 1992). Since the skull cannot expand, cerebral oedema may result in increased intracranial pressure (Ashwal *et al.* 1990), although most patients who present with MM have only a mildly raised Intra Cranial Pressure (ICP) (Odio *et al.* 1991). The mortality rate of 1%

to 2% is often due to severe cerebral oedema leading to herniation (Conner and Minielly 1980;Nassif *et al.* 2002;Stephenson 1998).

Due to the proliferation of meningococci in the meninges (see Figure 1.3) (Herrick 1919;Nassif and So 1995) high concentrations of endotoxin (van Deuren *et al.* 1995) tend to result.

Figure 1.3 – High concentration of meningococci and endotoxin in cerebrospinal fluid

Source : http://www.stephensanigfoundation.org.au/thedisease.php

1.5.3.2 Meningococcal Septicaemia

Meningococcal septicaemia (MS) can kill more rapidly than arguably any other infectious disease and without meningitis is the most fatal of the meningococcal syndromes, occurring with higher frequency during adolescence (Harrison *et al.* 2001;Harrison and Broome 1987). Early recognition is critical to implement prompt antibiotic therapy and supportive care. The case fatality rate can be as high as 53% in severe cases (Kirsch *et al.* 1996).

MS develops very rapidly with some patients progressing to fulminant septic shock requiring full intensive care support within 24 hours. MS is characterised by abrupt onset of fever, malaise, myalgia and sometimes headache, and sometimes seizures. It is characterised by a purpuric or petechial rash (although in some cases this does not appear until the disease is quite advanced), which may progress to fulminant septicaemia. This involves the rapid proliferation of meningococci in the circulation (see Figure 1.4), resulting in high concentrations of meningococcal endotoxin (van

Deuren *et al.* 2000). The severity of MS has been shown to be directly related to levels of circulating endotoxin (Brandtzaeg *et al.* 1989a;Brandtzaeg *et al.* 1989b; Brandtzaeg *et al.* 1992).

Figure 1.4 – Rapid proliferation of meningococci in the bloodstream

Source : http://www.stephensanigfoundation.org.au/thedisease.php

When purpura fulminans occurs, some tissues are irreversibly destroyed due to thrombosis within the microvasculature, combined with vasoconstriction and ischaemia in peripheries. Haemorrhagic necrosis in skin and clotting in small vessels can lead to loss of skin, digits or limbs.

Hypotension, acute adrenal haemorrhage (Waterhouse-Friderichsen syndrome), and profound shock also characterise fulminant MS (Brandtzaeg *et al.* 1989a;Brandtzaeg *et al.* 2001;Brandtzaeg 2006; Hackett *et al.* 2002). Shock is caused by capillary leakage, inappropriate vascular tone, intravascular micro thrombi, and myocardial dysfunction leading to hypotension and a reduction in circulation in most parts of the body, resulting in loss of consciousness and multi organ failure (Rosenstein *et al.* 2001). It is very difficult to correct the shock and other effects of endotoxin with treatment which is the reason that so many people with MS die (Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre 2001).

Approximately half of patients (Roos *et al.* 1997) and more specifically children and young adults (Anderson *et al.* 1997) develop a prominent petechial or purpuric rash, primarily on the extremities when the bacteria enter the bloodstream and multiply uncontrollably. This damages the walls of the blood vessels and causes bleeding into

the skin. The rash may start as a faint pink rash or as red or purple pinpricks on the skin and then develop into the distinctive purple lesions (see Figure 1.5).

Figure 1.5 – Progression of petechial and purpuric rash

Source : http://www.stephensanigfoundation.org.au/thedisease.php

A recent study of 448 patients examined the clinical recognition of MD in children and adolescents aged <16 years (Thompson *et al.* 2006). It identified three important clinical features before admission to hospital: leg pain, cold hands and feet and abnormal skin colour – that are signs of early MD in children and adolescents. These symptoms generally occur within the first 12 hours of the onset of MD. Cold hands, feet, and abnormal skin colour are features of early sepsis that represent changes in the peripheral circulation. In light of the findings, the authors argued for a diagnostic paradigm shift in order to speed up diagnosis as the classic symptoms of rash, meningism and impaired consciousness generally occur later in the pre-hospital illness and that primary care clinicians are over-reliant on using these three symptoms to diagnose MD in children. They further stated that parents may be influenced by doctors or public health campaigns to seek medical advice only on the appearance of features such as rapidly evolving rash and consequently clinicians and parents may be falsely reassured by the absence of these features.

1.5.3.3 Mild systemic meningococcal infection

Mild systemic meningococcal infection occurs more frequently than fulminant disease and is defined by the presence of meningococci in the blood and the absence of septic shock, distinct meningitis, or both. Provided that antibiotics are given before shock develops , there is low mortality (Brandtzaeg *et al.* 2001;van Deuren *et al.* 2000).

1.5.3.4 Localised meningococcal syndromes

Less commonly, individuals may present with metastatic and local infections in various sites of the body. For example, up to 15% of patients with MD present with pneumonia (Griffiss *et al.* 1991;Racoosin *et al.* 1998;Rosenstein *et al.* 1999). Meningococcal pneumonia occurs principally in immunocompromised or elderly patients (5%–15% of cases), (Blaser *et al.* 1984;Schaad 1980; Stephens *et al.* 1995; Wells and Gibbons 1997).

Others can present with conjunctivitis, myocarditis, otitis media, epiglottis or arthritis (Schaad 1980). Endophthalmitis, and cellulitis have been reported occasionally (Lin *et al.* 1995;Odegaard 1983;Sleep and Graham 1997), while adenitis, or pelvic inflammatory disease have also been reported (Anderson and Lind 1994;Ball and Young 1974;Barquet *et al.* 1990;Cher *et al.* 1993;Gelfand *et al.* 1998;Sacks 1986).

Shock is usually absent and almost all patients can be cured with antibiotics. Occasionally such infections may be preceded by invasive disease or may cause secondary cases.

1.6 Prevention

1.6.1 Chemoprophylaxis

The principal way to prevent secondary MD is antimicrobial chemoprophylaxis of close contacts of an infected patient, for example household members and anyone who has been directly exposed to an infected person's oral secretions (Connolly and Noah 1999; Rosenstein *et al.* 1999). Although the risk to contacts is low, the highest documented absolute and relative risk is to people who live in the same household as a case of MD (De Wals *et al.* 1981;Hastings *et al.* 1997). The case is likely to have acquired the invasive strain from a close contact, typically in the same household, who is an asymptomatic carrier. (Cartwright *et al.* 1991b; Kristiansen *et al.* 1998).

Chemoprophylaxis aims to reduce the risk of invasive disease by eradicating carriage in the group of close contacts at highest risk. Close contacts of the index patient are more likely to harbour virulent meningococci in their nasopharynx

(The Meningococcal Disease Surveillance Group 1974).

However, chemoprophylaxis needs to be commenced as soon as possible, ideally within 24 hours after identification of the index patient and certainly not more than 14 days after the onset of MD as thereafter it has been found to have little or no benefit (Advisory Committee on Immunization Practices 1997). The highest risk of secondary infection in untreated households is observed in the first 48 hours after onset of the disease in the index case (De Wals *et al.* 1981).

Rifampin, ciprofloxacin, and ceftriaxone have demonstrated 90-95% efficacy in reducing nasopharyngeal carriage (Rosenstein *et al.* 2001;van Deuren *et al.* 2000).

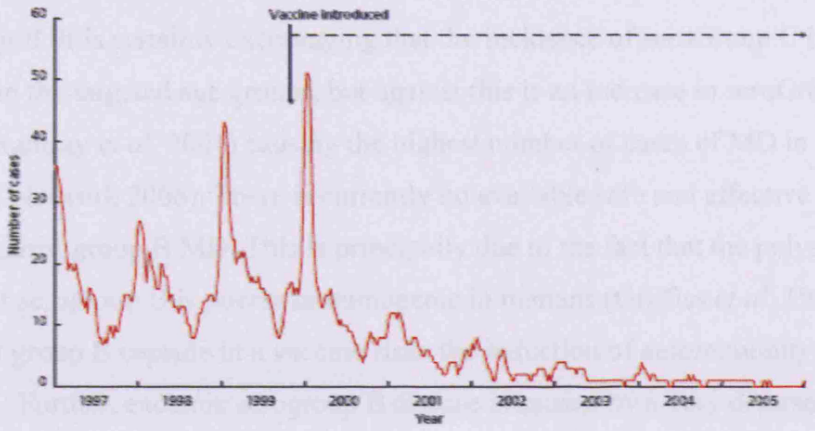
1.6.2 Vaccination

In the long term, the ultimate solution is prevention of MD by vaccination. A number of vaccines have been developed to protect against some forms of MD.

Vaccines come in two forms: polysaccharide vaccines, which consist of chains of sugar molecules derived from the surface of the corresponding organism, and conjugate vaccines, in which the same sugar molecules are chemically linked to a purified protein. The polysaccharide *Neisseria meningitidis* (meningococcal) vaccines are either bivalent (protecting against serogroups A and C) or tetravalent/quadrivalent (protecting against serogroups A, C, W135 and Y). The only current meningococcal conjugate vaccine is MenC, protecting against seroGroup C.

The increase of MD in teenagers in the mid to late 1990s, together with a higher case fatality rate in the 15-19 year age group, (Connolly and Noah 1999; Harrison *et al.* 2001) was a major stimulus in the United Kingdom for introducing the conjugate meningococcal serogroup C vaccine. The UK was the first country in the world to introduce mass vaccination against group C using a vaccine which is immunogenic in infants and primes for memory (Richmond *et al.* 1999). The vaccine known as MenC was introduced in the UK childhood vaccination programme in November 1999 (Miller *et al.* 2001) and applied to all under the age of 18 years. This was eventually extended to all under 25s in 2002.

Figure 1.7 – and **Laboratory weekly reports of meningococcal C disease in England Wales 1997-2005**



Source: Health Protection Agency

Ireland, Spain, Luxembourg, Belgium, and the Netherlands have also started immunisation programmes with a conjugate vaccine against *Neisseria meningitidis* serogroup C MD. In 2006, studies showed that protection against meningococcal group C wanes during the second year of life (Trotter *et al.* 2004), therefore a booster dose (combined with Hib as Hib/MenC) was introduced at 12 months of age.

Vaccines that offer protection against different strains of MD include the quadrivalent polysaccharide (non-conjugated) vaccine made from the outer capsules of seroGroup A, C, W-135 and Y meningococci organisms. This vaccine has been recently introduced (2005) in the USA for adolescents (Bilukha and Rosenstein 2005). A serogroup A conjugate vaccine is currently under development which has important implications for alleviating disease caused by this strain in sub-Saharan Africa (Soriano-Gabarro *et al.* 2004). Protection against serogroup C infection is believed to be of a shorter duration than that conferred by the conjugate vaccine, and the level of protection is inferior in young children. The protection conferred by the quadrivalent vaccine against seroGroups Y and W135 infection is inferred by the evidence of immunogenicity in adults. Therefore, efficacy in younger children is unknown, but expected to be similar to protection against serogroup C disease.

The ACWY vaccine is now a visa requirement for Muslim pilgrims to Mecca and recommended for travel to certain countries in Sub-Saharan Africa.

Serogroup B: It is certainly encouraging that the incidence of seroGroup C has declined in the targeted age groups, but against this is an increase in seroGroup B disease (Ramsay *et al.* 2001) causing the highest number of cases of MD in the UK (EU-IBIS Network 2006). There is currently no available safe and effective vaccine to protect against group B MD. This is principally due to the fact that the polysaccharide capsule of serogroup B is poorly immunogenic in humans (Griffiss *et al.* 1991), and the use of group B capsule in a vaccine risks the induction of autoimmunity (Finne *et al.* 1983). Further, endemic serogroup B disease is caused by a very diverse group of strains, which complicates vaccine development (Harrison 2006).

As a direct response to national epidemics of serogroup B in Norway and Cuba, vaccine research has focused on preparations of outer-membrane proteins (OMPs) that are mostly strain-specific (Poolman 1995;Verheul *et al.* 1993). Efficacy of B vaccines are restricted to a limited range of strains (Danzig 2004;Girard *et al.* 2006). Furthermore, large-scale trials in Chile, Cuba, Norway, and Brazil have yielded different success rates (Bjune *et al.* 1991;De Moraes *et al.* 1992; Milagres *et al.* 1994;Sierra *et al.* 1991;Zollinger *et al.* 1991). Low efficacy has been observed in children younger than 4 years, which is the age group with the highest incidence of seroGroup B (De Moraes *et al.* 1992; Noronha *et al.* 1995). Scientists in Italy, the USA and the UK (Oxford) are currently applying a genomic approach to the solution but it will be a number of years before an effective vaccine against serogroup B is developed. SeroGroup B therefore still poses a large threat to adolescents in the UK with 111 cases reported in 15-19 year olds in 2004 in England and Wales (EU-IBIS Network 2006).

1.7 Treatment

MD is a medical emergency and there are very few conditions in medicine that will progress as quickly, in some cases only a few hours. Patients with either meningococcal septicaemia or meningococcal meningitis must be hospitalised. Admission to intensive care may be required in severe cases. Early recognition of

meningococcal infection is critical as septicaemia spreads so quickly that within hours of symptoms appearing, a patient may rapidly die. The speed with which the diagnosis is made, antibiotics administered, and the complications of shock and multi-organ failure treated is likely to be a major determinant of outcome (Nadel *et al.* 1998). With early diagnosis and treatment, however, the likelihood of recovery is increased.

1.7.1 Pre-hospital antibiotics

General practitioners in the United Kingdom are currently expected to carry benzyl penicillin in their emergency bags and to administer prior to hospital admission whenever they suspect a diagnosis of MD. A recent review of 14 observational cohort studies was conducted to examine the evidence for the effectiveness of antibiotic treatment before admission and the impact on survival of patients with MD (Hahne *et al.* 2006). The authors found that oral antibiotics given before admission showed consistently improved survival among patients with MD who received such treatment compared with those who did not. Evidence from other studies supports pre-hospital antibiotic treatment in suspected cases of MD and has been shown to reduce case fatality in children by 40% (Cartwright *et al.* 1992;Cartwright and Kroll 1997; Gossain *et al.* 1992;Strang and Pugh 1992).

Benzyl penicillin should be started as early as possible and be the first action. This is a life saving aspect of management. Penicillin immediately stops the multiplication of meningococci (Brandtzaeg *et al.* 1989a;Brandtzaeg *et al.* 2001;van Deuren *et al.* 2000).

In 1944, the first successful treatment of meningitis with intravenous and intrathecal penicillin was reported, and the first clinical trails using high doses of intravenous penicillin for the treatment of meningitis were reported in 1950. Since then, penicillin has remained the drug of choice for the treatment of MD. Very severe cases of MD are often treated with both penicillin and cephalosporins prior to obtaining the laboratory results. If the patient has a history of anaphylaxis, chloramphenicol or injectable cephalosporin are alternatives. However, Chloramphenicol resistance has been reported (Galimand *et al.* 1998). It is important to give injectable medication, as

most patients given oral medication will vomit afterwards. Therefore, IM antibiotics are the key to early management of the disease.
In contrast, two recent studies from Denmark reported a twofold to threefold increase in mortality associated with antibiotics given before admission (Norgard *et al.* 2002;Sorensen *et al.* 1998). However, in a more recent study exploring the impact on mortality and morbidity of parenteral penicillin given to children before admission to hospital with suspected MD found that the children who were given parenteral penicillin by a GP had more severe disease on reaching hospital than those who were not administered penicillin before admission. The authors concluded that the association with poor outcome may be because children who are more severely ill are being given penicillin before admission (Harnden *et al.* 2006).

Before the 1920s, MD was fatal in up to 70 percent of cases (Flexner 1913). After the introduction of treatment with antibiotics such as benzyl penicillin, and cephalosporins, case fatality fell to around 10% and has remained so ever since.

Therefore, treatment with antibiotics is the only course of action for MD, combined with supportive treatment such as intravenous fluids to treat shock and prevent organ damage, medications such as noradrenaline (norepinephrine) for patients with very low blood pressure, blood products such as platelets and fresh frozen plasma, oxygen and ventilation by a machine to assist with breathing.

Patients who survive very severe cases of meningococcemia may have suffered severe necrosis of skin and underlying tissue. Skin grafts and amputation may be necessary.

1.7.1.1 Meningococcal Septicaemia

The first assessment of meningococcal septicaemia involves examining if shock is present. If the patient has cold peripheries, prolonged capillary refill, tachycardia, confusion, history of not passing urine for some time, all indicating signs of shock, then aggressive resuscitation needs to be initiated with rapid administration of antibiotics. A third-generation cephalosporin (e.g., cefotaxime, ceftriaxone) can be used initially in septic patients while the diagnosis is being confirmed or in countries such as the United Kingdom or Spain, where penicillin-resistant strains of *N meningitidis* have been isolated. In addition, vascular access is established to facilitate

the administration of volume expanders and inotropic medications needed for adequate tissue perfusion.

In patients with Fulminant Meningococcal Septicaemia (FMS) and Waterhouse-Friderichsen syndrome due to low cortisol levels they are likely to benefit from glucocortoid supplementation (O'Brien and Morton 1998) or dexamethasone. Intensive supportive care is required for patients with FMS. Treatment is individualised depending on the severity of the patient. In FMS 50% of patients die within the first 12 hours (van Deuren *et al.* 2000).

1.7.1.2 Meningococcal Meningitis

In the absence of imminent cerebral herniation or shock, treatment of uncomplicated meningococcal meningitis demands only parenteral antibiotics and close monitoring. The primary goal of therapy is to achieve a rapid bactericidal effect in the CSF. Some investigators have suggested that antibiotics exacerbate meningeal inflammation by stimulating endotoxin release, (Mustafa *et al.* 1989), and have therefore suggested postponing antibiotic treatment until after dexamethasone was given (Schaad *et al.* 1995). The administration of corticosteroids in patients with sepsis or bacterial meningitis is controversial (de Gans and van de Beek 2002).

Studies have shown that optimised transport to and prompt treatment at specialised units by an experienced team have resulted in lower case-fatality rates in children (Booy *et al.* 2001).

In a national blinded case-control study including 498 children (aged <17 years), the standard of care in the first 24 hours after admission to hospital was compared in children who died from MD and those who survived. Three factors were independently associated with an increased risk of death: not being cared for by a paediatrician, unsupervised junior staff, and failure of staff to administer adequate inotropes (Ninis *et al.* 2005).

1.8 Other causes of bacterial meningitis

Whilst this study only examines the bacterium *Neisseria meningitidis* causing MD, a number of different bacteria have the potential to cause meningitis. In the UK, *Neisseria meningitidis* and *Streptococcus pneumoniae* (causing pneumococcal meningitis) are the leading causes of bacterial meningitis with *Neisseria meningitidis* by far the most common cause after the neonatal period (Segal and Pollard 2004).

Haemophilus influenzae type b (Hib), once an important cause of meningitis in children under 5, has become uncommon in industrialised countries since the introduction of the Hib vaccine from the late 1980s (Adams *et al.* 1993).

Group B *Streptococcus* is the leading cause of neonatal meningitis in the UK with other causes for example, Listeria accounting for a small number of cases overall (Segal and Pollard 2004) – see Figure 1.8.

Figure 1.8 – Notifications of specific causes of meningitis in England and Wales 1990-2000

Source: (Segal and Pollard 2004)

1.8.1 Pneumococcal meningitis

Pneumococcal meningitis is caused by the bacterium *Streptococcus pneumoniae*. *Streptococcus pneumoniae*, also known as the pneumococcus, causes over one million deaths globally in children aged under five years (Leowski 1986). In the UK, reported

rates are 26/100,000 for the first five years of life (Sleeman *et al.* 2001), with around 30% of these cases presenting as meningitis (Shackley *et al.* 2000).

Streptococcus pneumoniae is the second most common cause of bacterial meningitis after *Neisseria meningitidis* in children under 2 years of age (Schuchat *et al.* 1997). There are at least 90 different strains, or serotypes, of pneumococcal bacteria, based on differences in the bacterial polysaccharide or 'sugar coat'. However, most disease is caused by only a few strains (Department of Health 2004a).

Reported rates of *S. pneumoniae* in the UK are 183 per 100,000 in the first week of life, and 26 per 100,000 for the first five years of life (Sleeman *et al.* 2001), with approximately 30% of cases presenting as meningitis (Shackley *et al.* 2000). The highest incidence is found in children less than 2 years of age. Incidence decreases in subsequent age groups to a low level in young adults but again increases in the elderly due to health conditions that compromise the immune system.

During 2000, 4744 laboratory isolates of *S. pneumoniae* from blood, CSF or other normally sterile sites were reported to the Health Protection Agency Communicable Disease Surveillance Centre (HPA CDSC) from laboratories in England and Wales (George and Melegara 2003).

Pneumococcal meningitis causes greater morbidity and mortality than most other types of bacterial meningitis, with death rates as high as 30%, compared to 3–13% for meningococcal meningitis, (Baraff *et al.* 1993;Grimwood *et al.* 1996;Laupland *et al.* 1998;Neuman and Wald 2001; Short and Tunkel 2000;Usen *et al.* 1998). Pneumococcal meningitis may affect individuals of any age, but is seen most frequently at the extremes of age, in very young children and in elderly adults. Death rates are highest in very young children and in elderly patients and those with serious conditions such as chronic illness or impaired immunity. Often pneumococcal meningitis is not accompanied by septicaemia.

Furthermore, survivors of pneumococcal meningitis are more likely to have after effects and have the highest rate of complications of all meningitides, with a higher risk of permanent neurological damage, spasticity / paresis, also epilepsy and of

particular importance hearing problems that often are bilateral and profound (Baraff *et al.* 1993;Jadavji *et al.* 1986; Kornelisse *et al.* 1995).

In developing countries, *Streptococcus pneumoniae* is one of the most important causes of severe illness and death in young infants (World Health Organisation. 1999).

Antibiotics are the cornerstone of treatment for pneumococcal meningitis but in the UK prevention by vaccination started in 2002, when a pneumococcal conjugate vaccine became available and recommended for immunisation of at-risk groups under the age of two years. In 2004, the conjugate vaccine policy was extended to at-risk children under five years of age. In 2003, pneumococcal polysaccharide immunisation was recommended for all people aged 65 years and over. In Scotland and Northern Ireland, the vaccination scheme has already been implemented in full. In England and Wales, the vaccination programme was phased in over three years (Department of Health 2004a).

1.8.2 Meningitis caused by *Haemophilus influenzae* type B (Hib)

Haemophilus influenzae (Hib) disease is the term used to describe infections caused by the group of bacteria *Haemophilus influenzae*. There are six strains of *Haemophilus influenzae* bacteria known to cause disease. The strain that used to cause the most disease in the UK is type b, usually referred to as Hib. Hib is spread by coughing, sneezing or close contact with an infected person. Hib is an infection that can present as meningitis, septicaemia and pneumonia, all of which are fatal if not treated quickly.

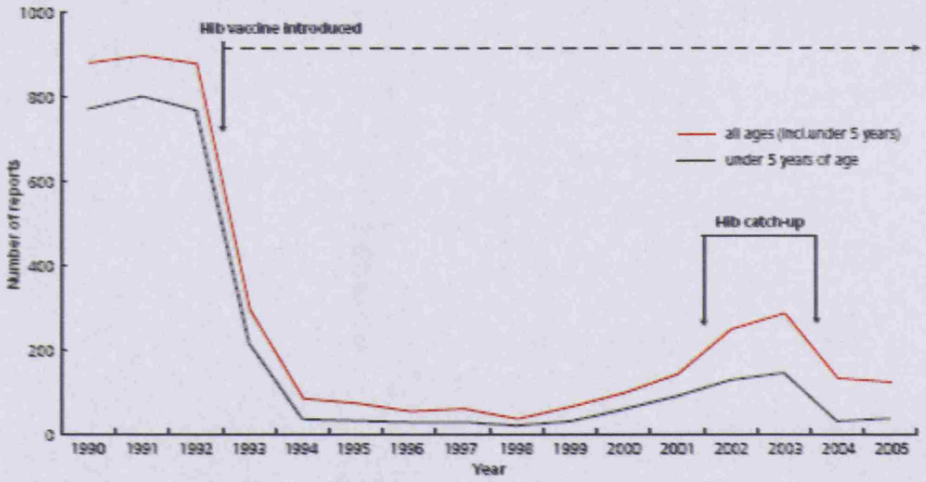
Prior to the availability and introduction of conjugate vaccines in October 1992, approximately one in 600 children developed some form of Hib disease by their fifth birthday (Booy *et al.* 1993;Howard *et al.* 1991). Children under four years of age were at most risk from Hib disease. More than two-thirds of cases were in children less than two years of age and those most at risk were infants aged 10–11 months (Booy *et al.* 1993).

Hib infection was the most common cause of bacterial meningitis in children in England and Wales. Studies in the US found that up to 45 children in every 100 suffered long-term neurological problems following Hib meningitis (Sell, 1987). There were around 30 deaths every year in England and Wales and about 80 children were left with deafness and permanent brain damage (Howard *et al.* 1991; Tudor-Williams *et al.* 1989).

Hib infections fell dramatically with the implementation of the vaccine programme in the UK (see Figure 1.9) and has remained at very low rates, although, a slight resurgence in cases was noted in 2003 which led to with a Hib booster vaccine campaign for children less than four years of age. The vaccine is now given to children as part of their routine immunisations which has resulted in Hib being virtually eliminated in the UK, North America, northern Europe, Australia, and New Zealand (Robbins *et al.* 1996).

Whilst Hib meningitis has been virtually eliminated in developed countries, in developing countries it is still a leading cause of bacterial meningitis, responsible for over 200, 000 cases and more than 40 000 deaths annually (Mulholland *et al.* 1997;Salisbury 1998). Ninety per cent presenting with Hib meningitis are under 5 years of age and the peak age group affected is 6-11 months. The case fatality rate is approximately 5-20% with complications occurring in approximately 20-30%, the most common being hearing loss (Salisbury 1998).

Figure 1.9 – Laboratory reports of Hib disease in England and Wales 1990-2005



Source: Health Protection Agency

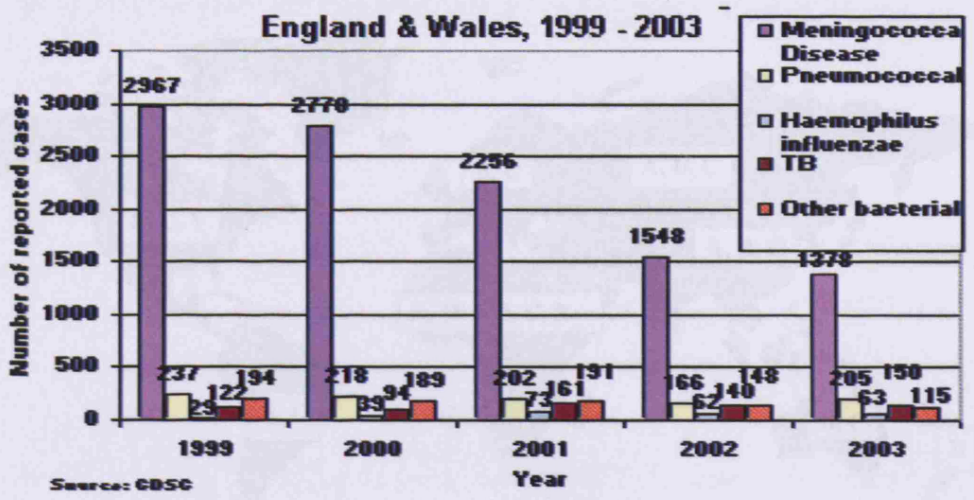
Reported cases of MD and other bacterial meningitis in England and Wales from 1999 to 2003 are shown in Figure 1.10, showing that meningococci caused the most disease.

The "other bacterial" category includes mainly uncommon types which are not counted separately, e.g. Group B *Streptococcal* (GBS), E. coli, and *Staphylococcal.*

1.8.3 Other bacterial causes of meningitis

Examples of other bacteria causing meningitis include *Mycobacterium tuberculosis,* which is comparatively rare. Those at risk include the elderly and those who have an underlying Tuberculosis infection. The infection starts usually in the lungs and travels to the brain via the bloodstream. It develops much more slowly than other bacterial forms and can be difficult to diagnose. The Bacillus Calmette-Guerin (BCG) vaccine is routinely given to all children in the UK and has shown to be 77% effective against disseminated tuberculosis (Colditz *et al.* 1994). *Group B Streptococcal* (GBS) - is a common cause of severe early (less than seven days of age) infection and can cause sepsis and meningitis. Currently, antenatal antibiotic therapy is the main preventative strategy (Segal and Pollard 2004).

Figure 1.10 – Reported cases of MD and other bacterial meningitis



1.9 Epidemiology of Meningococcal Disease

1.9.1 General Overview

The epidemiology of MD is serogroup specific and surveys have revealed that a few specific pathogenic clonal complexes spread the disease worldwide (Wang *et al.* 1992). Characterising strains involved in invasive disease is an essential aspect of epidemiological surveillance.

The distribution of five clinically significant strains (A, B, C, Y, and W-135) are responsible for approximately 95% of infection worldwide, with B and C responsible for the majority of cases in developed countries, including the UK, the rest of Europe and the Americas (Raghunathan *et al.* 2006; Rosenstein *et al.* 2001), see Figure 1.11.

Figure 1.11 – Global serogroup distribution of invasive MD

Source: (Stephens 2007b)

Within serogroups A, B, and C, most disease is caused by a limited number of groups of genetically related bacteria which have more recently been referred to as hyper invasive lineages (Maiden *et al.* 1998).

Annual incidence rates in developed countries are between 1-4/100,000 to 10-25/100,000 (Morley and Booy 1997). In sub-Saharan Africa where epidemics caused by serogroup A are frequent, incidence rates have been known to increase to well above 200 / 100,000 (Morley and Booy 1997). The divergence in incidence rates around the world reflects the different pathogenic properties of *N. meningitidis* strains and different geographical, socioeconomic, environmental, and climatological conditions that enhance transmission (Stephens 1999).

In developed countries, MD is endemic although small clusters occur affecting any age group. However, there is a distinct bimodal distribution in age with the greatest proportion of invasive MD occurring in children < 5 years of age (Cartwright 1999) followed by adolescents and young adults (Goldschneider *et al.* 1969; Ramsay *et al.* 1997).

Contrary to popular perception the adolescent peak of MD actually occurs in those younger than university age, with peak age 16-17 years in girls and 17-18 years in

boys (Jones and Mallard 1993). The highest mortality rates are in fact in teenagers aged 15-17 years of age (Harrison *et al.* 2001).

In endemic situations serogroup B is most common in infants, serogroup C in adolescents, and serogroups B or Y in older adults (Stephens *et al.* 2007b).

Molecular subtyping techniques, such as pulsed-field gel electrophoresis is one of the most widely adopted epidemiological tools for cluster designation, disease outbreak investigation, and tracking the global spread of meningococcal clones (Mayer *et al.* 2002; Mothershed *et al.* 2001). This technique has identified hyper-invasive lineages of *N. meningitidis* such as the electrophorectic type ET-37 clonal complex, whose origin can be traced back to 1917. This particular clone has caused widespread disease throughout the world for example, in the US, Brazil and China (Caugant 1998). The complex often expresses as serogroup C, but also may express as serogroup B, W-135 and Y. Some clones are genetically linked for example, serogroup W-135 was responsible for a global outbreak of MD in 2000 which was related to the Hajj pilgrimage in Saudi Arabia (Lingappa *et al.* 2003). It was found that the strain W-135 was derived from clonal expansion within the ET-37 complex and not from a new clone (Mayer *et al.* 2002).

In the last three years, no major changes in the prevalence of clonal complexes across Europe have been identified (EU-MenNet 2007).

Strains of the ET-5 complex represented mainly by serogroup B have spread globally and were responsible for the major epidemics in Europe in the 1970s and 1980s and in the United Kingdom, where the circulation of at least 3 subpopulation of this complex was reported (Bygraves *et al.* 1999).

In contrast to serogroup A or C epidemics, which usually resolve in 1 to 3 years, serogroup B causes substantial morbidity and mortality. It is associated with prolonged outbreaks (Stephens *et al.* 2007b) and may persist for 5 to 10 years or longer, as seen in Norway (Bjune *et al.* 1991) and areas of Chile (Boslego *et al.* 1995) and New Zealand (Martin *et al.* 1998).

In Europe, North America, Latin America and Australia/New Zealand the majority of sporadic cases are caused by serogroup B strains that are predominantly isolated in young children (Jones 1995). However, serogroup C has accounted for a higher proportion of cases of invasive MD in adolescents and young adults in recent years (Harrison *et al.* 2001). In the 1990s and early 2000s, outbreaks caused by virulent serogroup C clones were observed in Europe and North America, with a high proportion of fulminant septicemia cases occurring in adolescents and young adults, and case-fatality rates between 10% and 14% (De Wals 2006). As the only main serogroup for which still no general vaccine exists, the danger of a Men B in the developed world is still a serious threat.

1.9.2 Africa

The highest burden of MD is attributable to serogroup A disease, which since World War II has been a rare cause of disease in most industrialised countries (Rosenstein *et al.* 2001). However, serogroup A still causes recurrent epidemics in countries within the African "meningitis belt" and has been a significant public health problem for at least 100 years although it is believed to have been endemic for centuries in the West Coast of Sudan (Greenwood *et al.* 1985). Meningitis was first reported on the African continent as far back as 1909, by G William.

The "meningitis belt" was initially identified by Lapeyssonnie (Lapeyssonnie 1963). It extends across 15 countries (see Figure 1.12) with an estimated total population of approximately 300 million from Ethiopia in the east to Senegal and The Gambia in the west (Stephens *et al.* 2007b).

Figure 1.12 – African meningitis belt

Source: Centers for Disease Control and Prevention
http://wwwn.cdc.gov/travel/yellowBookCh4-Menin.aspx. Accessed 30th Aug 2007

In this area of Africa, epidemics of meningococcal meningitis occur almost every year in one or more countries in the region which may infect over 200,000 people at any one time with over 90% of cases presenting with meningitis alone (World Health Organization 2002).

1.9.3 Asia and Middle East

Asia has also been the focus of some major epidemics of MD over the last 30 years for example, China 1979 and 1980, Vietnam 1977, Mongolia 1973-74 and 1994-95, Saudi-Arabia 1987, and Yemen 1988 (van Deuren *et al.* 2000).

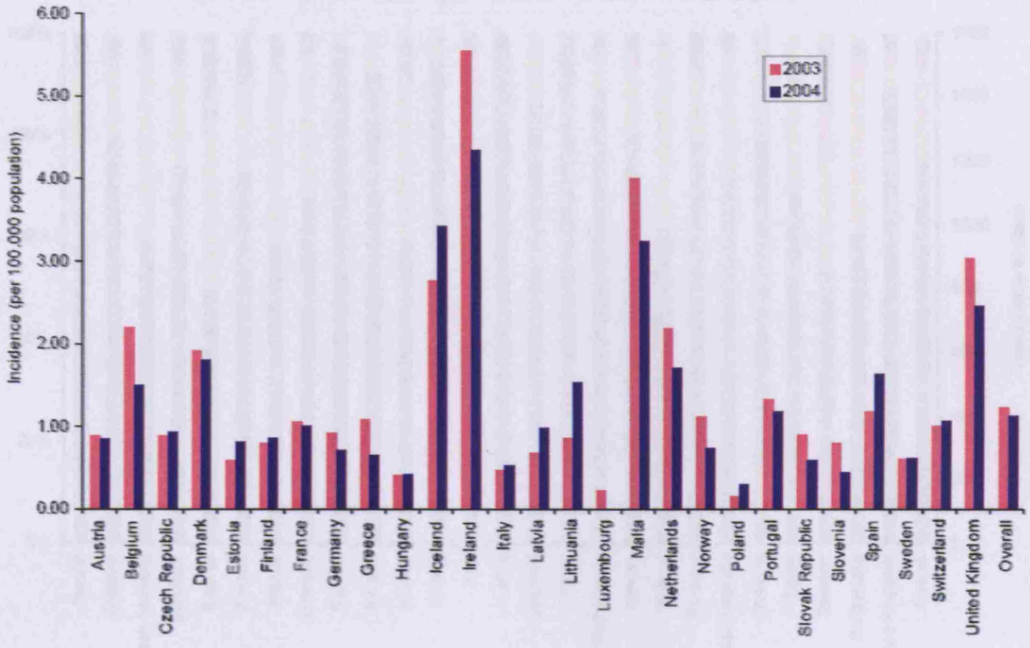
Epidemic disease has been associated with the annual Hajj pilgrimage to Mecca in Saudi Arabia for example, resulting in the spread of serogroup A meningococci during the late 1980s and the spread of W135 meningococci from 2000 onwards (Popovic *et al.* 2000). Pilgrims to Mecca became infected through close contact with large numbers of other pilgrims who then carried the bacteria back to their home countries resulting in importations into a number of countries around the world, including the UK. Two national outbreaks occurred in the UK due to W135 strains following the Hajj pilgrimages in 2000 and 2001 (Hahne *et al.* 2002). The quadrivalent (A,C,Y,W135) vaccine (introduced in 2005) is now required for entry into Saudi Arabia and as a result the number of W135 cases have returned to very low levels in the UK.

1.9.4 Europe

Outbreaks of MD occurring in Europe are much lower compared to the explosive outbreaks that occur in the Meningitis Belt (Rosenstein *et al.* 2001;World Health Organisation 2002a). Notwithstanding, there is considerable variability in the incidence of MD throughout Europe. For example, in 2004 incident rates ranged from 0.30 in Poland, 0.52 Italy to 3.42 Iceland and 4.35 Ireland (EU-IBIS Network 2006), see Figure 1.13.

The overall European incidence in 2004 was 1.13 per 100,000 population. Iceland and Ireland experienced very high rates of disease in 1999 (7.58 and 11.89 per 100,000 population respectively), however, these had decreased dramatically by 2004, though still considerably higher than those of most other European countries. The proportion of cases of serogroup C disease has dropped in those countries using MenC vaccine, including Belgium, Netherlands and the UK, but no decrease has been seen in Denmark and Norway, which have not introduced the vaccine into their immunisation programmes (as of writing September 2007).

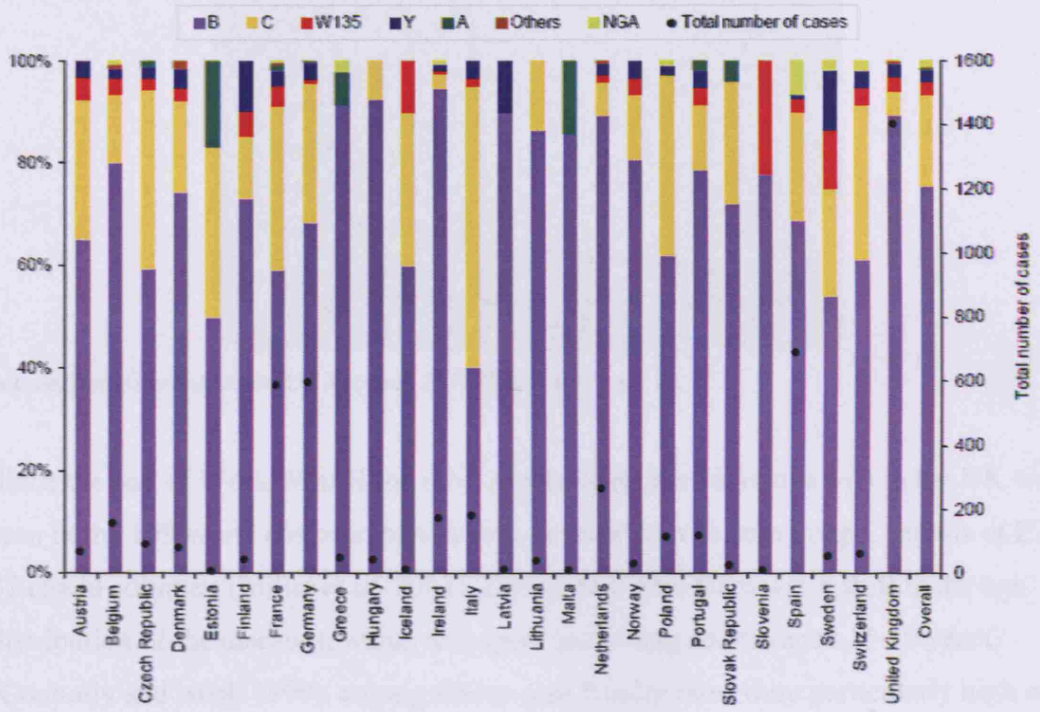
Figure 1.13 – Incidence (per 100,000 population) of laboratory-diagnosed confirmed and probable invasive MD in the European Union countries, 2003-2004



Source: European Union Invasive Bacterial Infection Surveillance Network(EU-IBIS Network 2006)

Serogroups B and C are the two main causes of invasive disease in Europe, contributing to approximately 90% of cases. An exception to this is Sweden, which has a relatively high proportion of serogroup W135 and Y isolates, although total numbers are fairly small (EU-IBIS Network 2006), see Figure 1.14.

Figure 1.14 – Percentage distribution of serogroups causing laboratory-diagnosed confirmed and probable MD in European countries, 2004



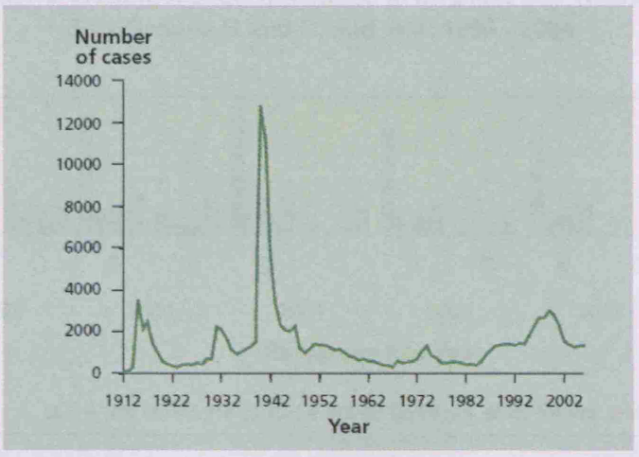
Source: European Union Invasive Bacterial Infection Surveillance Network (EU-IBIS Network 2006)

* NGA = non groupable

1.9.5 United Kingdom

Historically, large epidemics of MD in the UK were caused by serogroup A, however these have declined since World War II (see Figure 1.15) (Jones 1995). In recent years approximately 97% of cases of MD have been sporadic (Hastings *et al.* 1997;Ramsay *et al.* 1997) with less than 5% of cases occurring in clusters (Health Protection Agency 2007b). Invasive MD occurs throughout the year, however, the incidence of cases peaks mostly in the winter months, usually from November onwards, but can occur in the summer months to a much lesser degree. The reason why the incidence of MD is more common in winter than summer is not fully understood.

Figure 1.15 – Notifications of MD, England and Wales 1912-2002



Source: Department of Health, UK Accessed 25.08.07 at www.dh.gov.uk

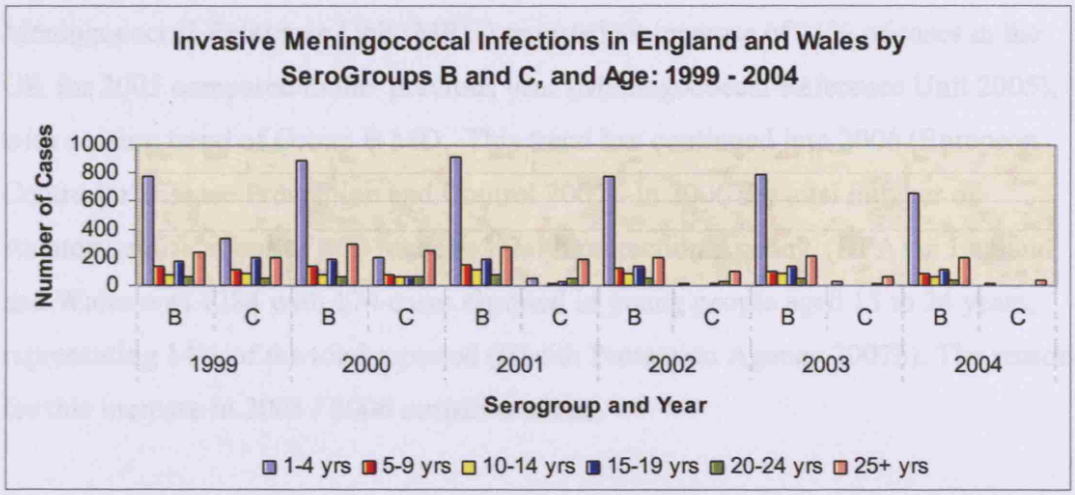
Since the end of World War II the most recent upsurge of invasive MD in the UK was seen in the 1990s and has been particularly associated with serogroup C strains of ET-37 clonal complex (Miller *et al.* 2001). During this time there was a shift in the age distribution of the disease towards teenagers and young adults (aged 15-19 years) (Connolly and Noah 1999), among whom case fatality rates were particularly high as they were more likely to have the septicaemic form of MD (Connolly and Noah 1999; Harrison *et al.* 2001).

As the rate of meningococcal serogroup C infections continued to rise in the UK, the development of the new vaccines progressed rapidly and in November 1999, the new MenC conjugate vaccine was introduced into the UK routine immunisation programme.

1.9.5.1 Current UK situation

Serogroup B disease continues to account for most [80%] of the reported cases of invasive MD in England and Wales today - a trend that is reflected across the UK (Health Protection Agency 2007b), see Figure 1.16.

Figure 1.16

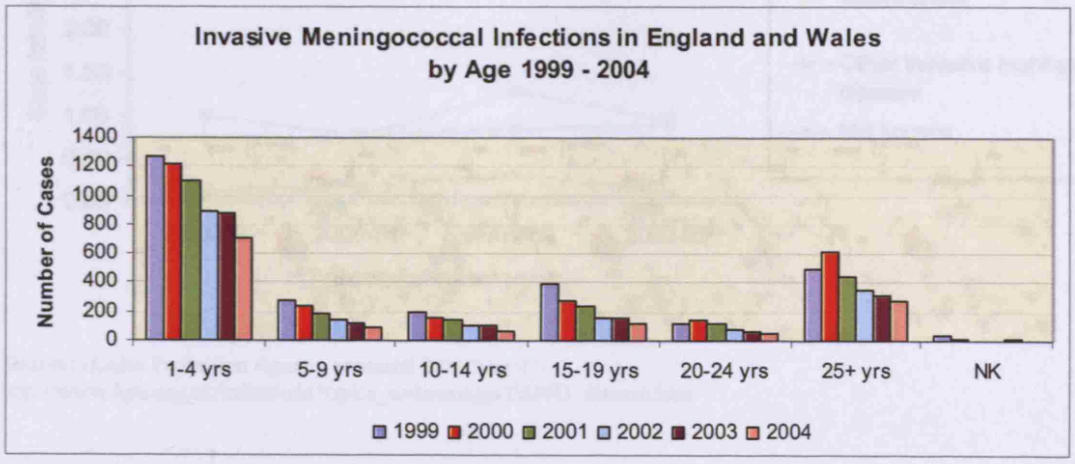


Data sourced from Health Protection Agency. Accessed 27.08.07
http://www.hpa.org.uk/infections/topics_az/meningo/data.htm

The average annual incidence of MD across the UK in 2004 was 2.46 / 100,000 population, which showed a marked decrease from 5.24 in 1999. Although the highest incidence was in children < 5 years, adolescents aged 15-19 years continued to have the second highest incidence of 3.7 /100,000, in 2004 (EU-IBIS Network 2006). This trend was consistent with overall patterns of the disease around Europe.

The proportional distribution of invasive MD by age groups and year is shown in Figure 1.17. In total 1,134 cases of MD were reported in England and Wales in 2004 (Health Protection Agency 2007a).

Figure 1.17

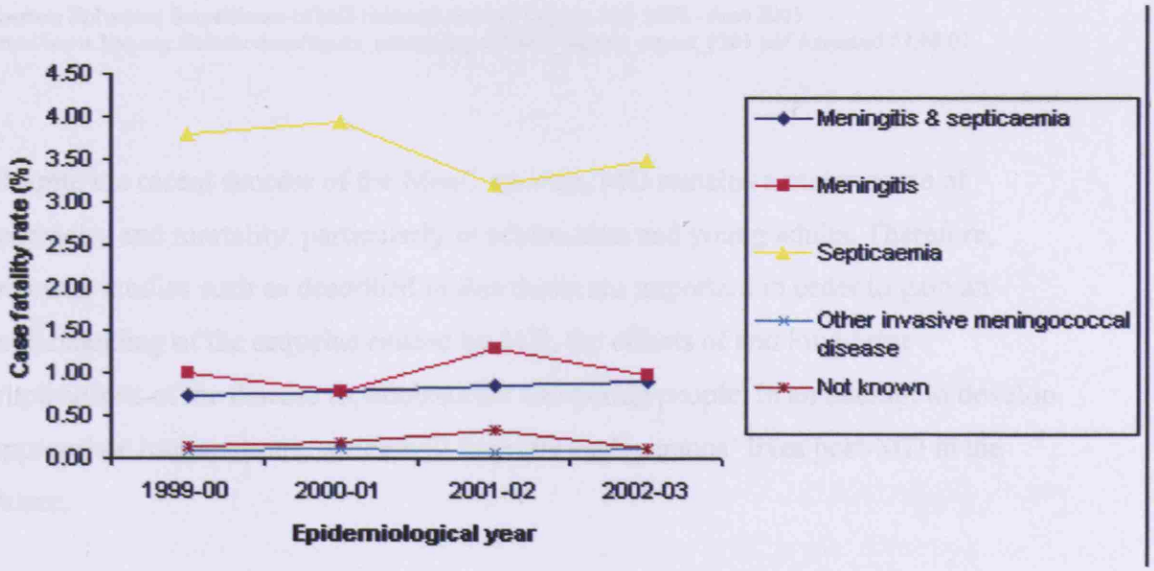


Data sourced from: Health Protection Agency. Accessed 27.08.07
http://www.hpa.org.uk/infections/topics_az/meningo/data.htm

However, despite the success of the MenC campaign, as discussed above, the Meningococcal Reference Unit (MRU) reported an increase of 11% of cases in the UK for 2005 compared to the previous year (Meningococcal Reference Unit 2005), with a rising trend of Group B MD. This trend has continued into 2006 (European Centre for Disease Prevention and Control 2007). In 2006 the total number of statutory notifications of MD made to Health protection Agency (HPA) in England and Wales was 1284 with 174 cases reported in young people aged 15 to 24 years, representing 14% of the total reported (Health Protection Agency 2007b). The reasons for this increase in 2005 / 2006 remain unclear.

Mortality in patients with invasive MD depends on the age of the patient, the clinical manifestation, clonal complex of the organism, and case management (Cartwright 1995b). Overall mortality in MD cases remains around 10% in the UK (Goldacre *et al.* 2003;Ramsay *et al.* 1997) but is higher in cases with septicaemia than in those with meningitis alone (Davison *et al.* 2002). See Figure 1.18 for the case fatality rates in England and Wales by syndrome from 1999 to June 2003.

Figure 1.18 – Case fatality rates of MD by syndrome in England & Wales, 1999 - 2003



Source: Health Protection Agency accessed 24th Aug 07.
http://www.hpa.org.uk/infections/topics_az/meningo/ESMD_disease.htm

In contrast to the incidence of MD, the Case Fatality Rates (CFRs) increase with age (as shown in Figure 1.19) (Goldacre *et al.* 2003;Ramsay *et al.* 1997) and in those infected with strains with certain typing patterns (Trotter *et al.* 2004).

Most deaths occur in adolescents and young adults. The CFRs increased in the 15-24 and 25+ age groups in 2002-03 compared to the previous year; however, the CFRs for the 1-4 and 5-14 age groups decreased when compared to year before.

Figure 1.19 – Case fatality rates for England, Wales and Northern Ireland in confirmed cases of MD by age group: 2001-02 and 2002-03

Source: Enhanced Surveillance of MD National Annual Report: July 2002 - June 2003
http://www.hpa.org.uk/infections/topics_az/meningo/ESMD_annual_report_0203.pdf Accessed 27.08.07

Despite the recent success of the MenC vaccine, MD remains a major cause of morbidity and mortality, particularly in adolescents and young adults. Therefore, outcome studies such as described in this thesis are important in order to gain an understanding of the sequelae caused by MD, the effects of and long-term implications of the disease to, adolescents and young people, in an attempt to develop appropriate interventions, which will improve such persons' lives post-MD in the future.

CHAPTER 2 – LITERATURE REVIEW: OUTCOMES OF MENINGOCOCCAL DISEASE

2.1 Introduction

Much is known about the pathophysiology and management of meningococcal disease (MD) in its acute stages. However, little is known of the long-term effects of MD and more specifically the effects of MD in adolescence. The little research that has been done in young people has shown that the proportion of individuals suffering significant long-term sequelae can be as high as 20% (Erickson *et al.* 2001). Few studies have focused on the septicaemic form of MD which is more prevalent in adolescents (Harrison *et al.* 2001).

Studies which have examined the outcomes of MD, have mostly focused on physical sequelae, particularly hearing loss, and have been conducted across all ages, with few studies including small numbers of adolescents. In addition, there are a number of studies, which have examined the outcomes of all causes of bacterial meningitis, and have included small samples of MD survivors. Once again, these studies have focused primarily on major physical sequelae in younger children. Consequently, the effects of MD in adolescence, particularly the possibility of damage to cerebral matter during a psychosocially vulnerable stage of life, are poorly studied.

What follows is a review of the literature that focuses primarily on reports that relate to outcomes caused by *Neisseria meningitidis*. In addition, studies that have concentrated on bacterial meningitis of all aetiologies are only reviewed here to the extent that specific findings related to MD had been reported. Findings from the studies on outcomes of MD specifically, are reviewed critically, as methodology and study samples vary considerably. The findings are considered under three separate headings: physical, neuropsychological and psychosocial outcomes.

Included in the review is a brief discussion on the possible effects of admission to an Intensive Care Unit (ICU), which may itself have an effect on the psychological outcomes in MD.

Search method of relevant publications

An extensive literature search for all scientific articles pertaining to the sequelae of MD and all causes of bacterial meningitis was conducted. A number of electronic databases were thoroughly searched for example, Medline and Psych Info. Searches were performed repeatedly throughout the course of my PhD studies. Medical Subject Heading Terms (MeSH) and/or relevant keywords were applied to searches. Reference lists from identified articles were also utilised to identify any additional studies and in addition, hand searches were conducted.

2.2 Design of outcome studies

Thirteen observational outcome investigations caused by the infection of *N.meningitidis* were identified for review (see Table 2.1).

Table 2.1 Table summarising the methodology of 13 MD outcome studies reviewed

Author	Year	Country	Type of Study	Case ascertainment	Follow-up evaluation	Recruitment of cases	Controls how recruited	Time since MD
Fellick et al	2001	UK	Case-Control	Retrospective	Prospective	Hospital series	GP matched (age & sex) controls	9-10 years
Drake et al.	2000	New Zealand	Cohort	Retrospective	Retrospective	Hospital series	N/A	6-12 weeks
Moss PD	1982	UK	Case-Control	Retrospective recruitment from hospital	Prospective	Hospital series (outbreak study)	Gender, grade and age matched controls from school roll	5-9 years
Harrison et al.	2001	USA	Population based surveillance	Retrospective	Retrospective	Population series	N/A	Not available
Edwards et al.	1981	USA	Cohort	Retrospective	Prospective	Hospital series	N/A	Not available
Erickson & De Wals	1998	Canada	Cohort	Retrospective (provincial register)	Partly retrospective and partly prospective	Population series	N/A	9-72 months (mean 38)
Judge et al.	2002	UK	Cohort	Retrospective	Prospective	Hospital series	N/A	3-12 months
Naess et al.	1994	Norway	Cohort	Retrospective	Prospective	Hospital series	N/A	Approx 1 year after hospitalisation
Erickson et al.	2001	USA	Cohort	Retrospective	Partly retrospective and prospective	Population series	N/A	Not available
Sander et al.	1984	Norway	Case-control	Retrospective	Prospective	Hospital series treating military patients	Age matched unaffected soldiers from same units as the cases	3-15 years (mean 8 years)
Djupesland et al.	1982	Norway	Prospective series	Case ascertainment from hospital	Prospective	Hospital series	Patients with meningitis by organisms other than NM were considered as controls	6 weeks
Dawson et al.	1990	UK	Cohort	Retrospective	Retrospective	Population series	N/A	Not available
Wang et al	2001	USA	Cohort	Retrospective	Retrospective	Population series	N/A	Not available

The studies were conducted in industrialised countries, and published in the English language. Few of the investigations included adolescent MD survivors. Four of the studies were conducted in the UK, 3 in Norway, 4 in the USA and one each in New Zealand and Canada. Methods used to investigate sequelae of MD were varied and therefore studies are critically reviewed and the following aspects discussed separately: study design encompassing the structural aspects of the study – notably, how participants were selected, study size, and timing of evaluations, the choice of outcome measures, and follow-up rate. Also discussed are exclusion criteria and the relevant findings.

2.2.1 Study type

The approach undertaken in studies to determine the outcome of any condition is crucial. In all 13 studies, cases were ascertained retrospectively. However, 7 studies evaluated participants prospectively. Studies that evaluated participants prospectively included: 3 case-controls studies (Fellick *et al.* 2001;Moss 1982;Sander *et al.* 1984) and 4 cohort studies (Djupesland and Gedde-Dahl 1983; Edwards and Baker 1981; Judge *et al.* 2002; Naess *et al.* 1994).

Two cohort studies (Dawson and Wardle 1990;Drake *et al.* 2000) and two population-based surveillance studies (Harrison *et al.* 2001; Wang *et al.* 2001) evaluated participants retrospectively.

The remaining two cohort studies evaluated participants both retrospectively (by examining medical records) and prospectively (by administering questionnaires and conducting telephone interview) (Erickson and De Wals 1998;Erickson *et al.* 2001).

Prospective studies have been shown to minimise selection bias (Sica 2006), and based on pre-determined criteria for case ascertainment, are likely to provide the most valid findings. The advantage of a prospective approach is that standardised clinical and laboratory investigations can be carried out, rather than having to rely on possibly incomplete historical case notes. However, with a retrospective approach, errors due to confounding and bias are more common than in prospective studies, particularly

selection bias because both disease outcome and exposure have already been ascertained at the time of participant selection (Hennekens and Buring 1987).

There are also difficulties in assessing outcomes based on non-standardised records in retrospective case ascertainment and follow-up evaluation as case notes must contain sufficient information for a specific diagnosis and evaluation to be made.

Four studies under review ascertained cases retrospectively and evaluated retrospectively. For example, Harrison et al, in a population-based surveillance study of MD in adolescents and young adults used case reports completed by a hospital infection control professional; microbiology laboratory reports; and a standardised chart abstraction form, when reviewing medical and health department records (Harrison *et al.* 2001). The method of using a standardised data collection tool to abstract data from medical records of MD cases was also used in another population-based surveillance study of 194 children aged <18 years from 4 paediatric centres in Boston, USA over a 16 year period (Wang *et al.* 2001).

In another study which assessed hearing in children after meningococcal meningitis 6 weeks post-discharge, cases were identified by searching medical records using International Classification of Diseases codes, microbiology reports, with outcomes determined by review of the medical, microbiology and audiological records (Drake *et al.* 2000). In the remaining study, which retrospectively evaluated hearing loss in a cohort of 50 children following MD with serogroup B, the medical records were again used to obtain information on cases. However, the authors do not provide sufficient detail on how data were abstracted from the records and whether a standardised method was employed (Dawson and Wardle 1990).

Exclusion criteria: Only three papers provide details of exclusion criteria for follow-up evaluation. It is important to identify such criteria as they may confound the findings. Fellick et al followed-up 115 children aged 1 month to 15 years at MD, 9-10 years later with age and sex matched controls in order to examine neurodevelopmental outcomes (Fellick *et al.* 2001). Subsequently, cases with major neurodevelopmental disability and controls that had previous meningococcal infection were excluded. Wang et al in a study of 194 child survivors of MD in Boston, USA

excluded children who did not have microbiologically confirmed MD (Wang *et al.* 2001).

The other study that stipulated exclusion criteria at follow-up evaluation assessed hearing in 65 children 6-12 weeks, post meningococcal meningitis. Understandably, cases with pre-existing neurological or sensorineural hearing deficit were excluded as well as survivors of meningococcal septicaemia. The study also excluded cases outside the geographical area of the study centre, which may limit the generalisability of the findings (Drake *et al.* 2000).

The remaining 10 studies did not provide any details on their exclusion criteria or the pre-existing health status of participants.

All studies however provided details on confirmation of diagnosis of MD which in all cases was based either upon growth of *N meningitidis* from blood or cerebrospinal fluid specimens and /or clinical presentation. Details on serogroups were provided by only 8 studies and clinical presentation of MD [meningitis only, septicaemia only or mixed disease] by 12 studies.

2.2.2 Study size

It is well known that small studies tend to be under powered and are unable therefore to detect an important difference in effect even if one is present (Pocock 1983). Unfortunately, no studies in this review reported power calculations. Therefore, findings from the smallest studies may underestimate the adverse effects of MD. Any selection process, regardless of sample size would need to ensure a sample that was representative in terms of factors such as age, sex and severity of illness to ensure that conclusions are generalisable.

Studies varied in their sample size with the number of participants at follow-up ranging from 25 (Erickson *et al.* 2001) to 420 (Erickson and De Wals 1998).

For example, the smallest study examined outcomes of MD in 25 US college students and found that 20% [n=5] reported permanent physical sequelae. However, age at MD

and time to follow-up were not stated and in the absence of such important details, coupled with the small size of the study, it is impossible to drawn any meaningful conclusions (Erickson *et al.* 2001).

Of the 13 studies under discussion, only 5 had samples of >100 participants (Djupesland and Gedde-Dahl 1983; Erickson and De Wals 1998; Fellick *et al.* 2001;Harrison *et al.* 2001; Wang *et al.* 2001). 4 studies had <50 participants, (Dawson and Wardle 1990;Drake *et al.* 2000;Erickson *et al.* 2001;Judge *et al.* 2002). The remaining four studies had samples ranging from 50-99 (Edwards and Baker 1981; Moss 1982;Naess *et al.* 1994; Sander *et al.* 1984).

2.2.3 Time interval to follow-up

Follow-up evaluations occurred at widely varying intervals ranging from 6 weeks to 15 years post-MD. All studies evaluated participants at a single time point.

A number of studies were interested in the longer-term outcomes of MD. For example, a Norwegian case-control study, followed-up 71 young male MD, survivors 3-15 years later. Age matched controls from the same military units were also recruited. No differences were found between cases and controls in the incidence of hearing loss, but neuropsychological disturbances and complaints about health were found in survivors (Sander *et al.* 1984).

Other studies have been more focused on outcomes in the short-term. For example, in a retrospective study of 65 infants and children (aged 6 weeks to 15 years at MD) hearing was assessed in 49 children (75%) 6-12 weeks post-meningococcal meningitis, and found a low rate (4.2%) of sensorineural hearing loss in those tested (Drake *et al.* 2000).

If the follow-up period is too long it can have a negative impact on the follow-up rate of the study, which in turn can affect the validity of the findings.

2.2.4 Loss to follow-up

Attrition can be problematic in most follow-up studies and can often lead to bias when subjects who are lost differ from those who remain in the study (Sica 2006). If the proportion of cases with sequelae in those lost to follow-up was substantially greater than in those studied, it would result in an under-estimation of sequelae and compromise the internal validity of the study. The more rare the condition is the more significant is the effect (Mann 2003).

In the studies reviewed, loss to follow-up was not specifically discussed but deduced from the original sample reported and the sample at follow-up. Rates of follow-up in 10 studies were within the generally accepted rate of 80%. Loss to follow-up rates ranged from 6% (Edwards and Baker 1981; Naess *et al.* 1994) to 17% (Fellick *et al.* 2001).

Three exceptions were noted: Loss to follow-up was high in two studies [25%] (Drake *et al.* 2000) and [27%] (Moss 1982). In another study, which examined outcomes in 102 survivors and 61 controls, the original sample of cases was not stated in the paper and therefore rates could not be assessed (Djupesland and Gedde-Dahl 1983).

2.2.5 Comparison groups

Selection of appropriate controls to avoid bias is a significant challenge for most researchers. Few, if any, succeed in identifying inter-alia two groups of subjects equal in age, gender, socioeconomic status, presence of coexisting illness, with the single difference being their exposure to the agent being studied (Greenhalgh 1997). Nevertheless, the control group needs to be as similar as possible to the affected group in order to allow a meaningful assessment of the outcomes. At the very least, cases should be matched in respect of potentially confounding variables, such as age and gender.

A comparison group were used in four of the studies under review and were recruited from a number of different sources. Sander et al, studied 71 young military recruits with a comparison group (n=64) recruited from the same units (Sander *et al.* 1984). A

study examining the neurodevelopmental outcomes of MD in 115 MD survivors aged 1 month to 15 years at disease and evaluated 9-10 year later, obtained the controls through the GP of the index case (Fellick *et al.* 2001). In drawing controls from the same geographic area as the case it is possible to reduce the bias of factors such as socioeconomic status (Wacholder *et al.* 1992c).

The third investigation which enrolled a comparison group to assess the outcome of meningococcal B meningitis in 60 children aged 1 month to nearly 8 years at disease, recruited age and sex matched controls who were classmates of the index case (Moss 1982). However, the number of controls recruited was not stated. In addition, both cases and controls were drawn from social classes IV and V, which question the generalisability of the findings to other social groups.

2.2.6 Methods of assessing outcomes

The most valid results arise from using test instruments that are standardised and validated with standard data collection procedures (Grimes and Schulz 2002a). Such an approach to data collection minimises interviewer bias and increases the reliability of the findings.

In the studies included in this review, the methods of assessment of outcomes varied considerably. A total of 8 investigations relied entirely on standardised tools in their evaluation of outcomes (Drake *et al.* 2000;Erickson *et al.* 2001;Fellick *et al.* 2001;Harrison *et al.* 2001; Judge *et al.* 2002;Moss 1982;Naess *et al.* 1994b; Wang *et al.* 2001).

Other studies were less clear in their description of assessment instruments. For example, in a study assessing the prevalence of hearing loss in a cohort of 50 children aged 2 months to 17 years at MD who were hospitalised with serogroup B meningococcal infection Dawson et al, did not define the type of hearing tests that had been conducted on participants (Dawson and Wardle 1990).

Furthermore, in a study conducted by Erickson et al, which examined outcomes in MD survivors of all ages, an unvalidated questionnaire was sent to participants who

were followed-up by telephone. Exactly how many survivors of group C or B disease responded to the questionnaires was not reported (Erickson and De Wals 1998).

The remaining three investigations used a combination of medical tests and/or examinations and unvalidated questionnaires (Djupesland and Gedde-Dahl 1983; Edwards and Baker 1981; Sander *et al.* 1984).

Ideally, assessors should be blinded to the status of the participant (case or control) as prior knowledge can consciously or subconsciously bias the assessor, which may result in an over-or-under estimation of the true measurement. If blinding is not feasible it is recommended that standardised, uniform data collection procedures are used in all subjects (Kopec and Esdaile 1990).

Only two studies discuss this issue. Sander et al, stated that they "*believed*" the examiners were "*ignorant as to whether the individual had experienced meningococcal disease or not*". How this was ascertained was not discussed (Sander *et al.* 1984). In contrast, Fellick et al, are clear and report that one researcher organised recruitment and therefore was not blind to the status of subjects (Fellick *et al.* 2001).

2.2.7 Definition of outcome

The definition of outcomes as well as the definitions of severity varies between studies. A particular adverse effect may be described and/or measured in different ways. In studies which have focused on a single outcome such as hearing loss (Dawson and Wardle 1990;Drake *et al.* 2000) or psychiatric adjustment (Judge *et al.* 2002), reporting of findings is fairly uncomplicated. However, when the emphasis is on multiple sequelae, researchers have assessed the overall severity of disability resulting from the outcomes. In such studies substantial detail regarding the method of classifying outcome is provided (Djupesland and Gedde-Dahl 1983; Fellick *et al.* 2001; Naess *et al.* 1994; Sander *et al.* 1984). For example, Edwards et al, classified significant outcomes in a cohort of 79 MD survivors aged <16 years at disease, as allergic or non-allergic with 27% of cases experiencing one or more problems falling into these two categories (Edwards and Baker 1981). Accordingly, a standardised

approach to the ascertainment of the severity of sequelae in outcome studies is suggested.

2.3 Risk factors for poor outcome

Identifying risk factors for poor outcome of MD survivors is essential to enable clinicians to prognosticate which groups of survivors who may in the long-term require support. In the studies under review, the risk factors for poor outcome were not studied systematically although a number of risk factors were identified. Seven studies in total discussed risk factors associated with poorer outcome.

Clinical factors

Edwards et al, reported in a cohort of MD survivors aged <16 years at disease that several clinical or laboratory features were predictive for the development of arthritis or cutaneous vasculitis (Edwards and Baker 1981). These included shock or purpura at admission, leukocytosis (20,000 WBC/mm3), or leukopenia (< 5,000/mm3) at admission and persistence of fever >than 38.3 C for longer than 5 days. Shock or purpura and leukocytosis (20,000 WBC/mm3) was also predictive of a poor prognosis. In addition, hearing loss was significantly associated with peripheral leukocytosis or leucopoenia at admission and a CSF fluid WBC of > 10, 000 mm3. Other studies have also found that clinical symptoms and laboratory factors, pre and during hospitalisation increased the likelihood of poorer outcomes. For example, Sander et al, reported that survivors (aged 18-24 years at MD), with a fever for more than 8 days on admission, and who had < 2.5 mmol/glucose and high WBC in their CSF, as well as cerebral symptoms were more likely to have a high rates of late sequelae (Sander *et al.* 1984).

Age and gender

An American population-surveillance investigation reported on a sample of 255 MD survivors, and found that young people aged 15-24 years were more likely to have the septicaemic form of the disease without meningitis, with infection caused by serogroup C and they were more likely to be male (Harrison *et al.* 2001). In addition, they found that cigarette smoking was reported as a risk factor for nearly half of the

young people in this age group and that nearly a quarter of meningococcal infections in 15 to 24 year olds were fatal. The authors suggest this is due to the high frequency of meningococcaemia in this age group. Meningococcal infection in survivors aged more than 25 years was associated with chronic conditions. However, since the survivors were not followed up prospectively after discharge from hospital but rather data on cases was obtained from medical and health department records, using a standardised chart abstraction form they may underestimate the frequency of certain sequelae.

Erickson et al, also found in a Canadian retrospective outcome study of MD on survivors of all ages n=420, which included a large sample of 10-19 year olds [n=231], that serogroup C disease produced high rates of complications in adolescents and young adults. Serogroup C also had a higher fatality rate than for group B (14% vs. 7%) respectively. Most complications found were caused by the septicaemic form of infection (Erickson and De Wals 1998).

In another study, Naess et al examined sequelae one year after MD in 93 children and adults and reported that sequelae were more common in adults than children (40% vs. 15%). They also found that neurological sequelae were more common in females than in males and audiological sequelae more common in males (Naess *et al.* 1994). This is consistent with the findings from another study which also reported a higher incidence of sequelae in females compared to males (Djupesland and Gedde-Dahl 1983).

2.4 Main findings on meningococcal disease from outcome studies

Findings from the studies thus far reviewed are discussed in this section with sequelae of MD and are considered under three headings: physical, neuropsychological and psychosocial outcomes.

2.4.1 Physical sequelae

Studies examining physical outcomes following MD have resulted in different rates of complications due to methodological variations as previously discussed, such as time

interval to follow up, outcome measures used, diagnostic tests used, differences in populations and age groups. Such differences render comparability across studies difficult.

Physical sequelae of MD may be neurological related to meningococcal meningitis or sequelae relating to meningococcal septicaemia, namely scarring, amputations, arthritis or vasculitis and renal failure. Indeed, most physical sequelae of MD result from the septicaemic form of infection (Erickson and De Wals 1998).

The risk of major physical sequelae in MD has been reported to be as high as 29% (Djupesland and Gedde-Dahl 1983; Naess *et al.* 1994). Most physical sequelae have been reported when septicaemia is present which has generally been shown to increase the risk of sequelae such as multiple organ damage, renal failure, scarring, amputations and arthritis. One of the most comprehensive studies reviewed examined physical sequelae following MD and was undertaken in Quebec, Canada (Erickson and De Wals 1998). It was the first study to examine the impact of MD on survivors using an objective physical injury scale (The Annotated Scale of Bodily Injuries Regulation, ASBIR). The scale enabled the researchers to calculate an overall score of permanent mental and physical impairment. The differing effects of serogroup B and C were also recorded. Over 400 cases of MD were evaluated of all ages (<1 year to > 60) which included survivors of seroGroup B (n=167, average age 13.5 years) and C (n=304, average age 17.6 years) who were followed up approximately 38 months post-MD. The largest age group of group C survivors was 10-19 year olds (n=101) and of group B survivors aged <1 year (n=72). The physical impairment score obtained from the ASBIR took into account anatomic and physiologic deficits, disfigurement and suffering resulting from the deficit or disfigurement.

Most complications were of septicaemia. High rates of physical sequelae were found such as scarring, amputations, hearing loss, and renal problems with 3% of serogroup B survivors and 15% of serogroup C survivors affected. 11.5% of group C survivors had scarring and 4.6% had amputations. These were the most common physical sequelae. Among those with sequelae, the average physical impairment score was 39% for group B and 55% for group C disease. The study noted particularly high rates of complications in adolescents and young adults who had MD caused by serogroup

C. The fatality rate of 7% was observed for serogroup B and 14% for serogroup C disease. For serogroup C cases, the maximum mortality and morbidity was seen in the 20-59 year age group and for serogroup B at the upper and lower extremes of the age scale.

Although the study was comprehensive, its main weaknesses are that it was uncontrolled and retrospective with data collected from the medical records of survivors from 91 different hospitals. Nevertheless, the findings are useful and provide indications of physical sequelae in adolescents and young adults post MD.

Higher proportions with physical sequelae in survivors with seroGroup C disease were also noted in a more recent retrospective study of MD amongst US college students (n=25) using the ASBIR. This study found that 20% of survivors had permanent physical sequelae due to seroGroup C, mainly due to complications of septicaemia. No physical sequelae were noted in those with serogroup B disease (Erickson 2001).

In contrast, an American population-surveillance investigation reporting on a sample of 255 MD survivors (Harrison *et al.* 2001) found that very few survivors aged 15-24 years, experienced long-term physical sequelae, only one survivor with bilateral below-the-knee amputation was reported and one with hearing loss. This was also reflected in survivors aged <15 years and those aged >25 years. This was surprising as the study found that this age group was more likely to have the septicaemic form of the disease, with infection caused by serogroup C and higher case fatality rates compared to younger survivors. However, as discussed previously, survivors were not followed-up prospectively after discharge from hospital but rather data on cases was abstracted from medical records, which may therefore underestimate the frequency of the sequelae.

Significant physical sequelae are found to be less common in younger children. A study of 194 child survivors of MD (aged <18 years) conducted in the US, reported that only 5 (2.6%) had amputation or scarring (Wang *et al.* 2001). This is consistent with an earlier case-control study of meningococcal meningitis survivors from 1982 (Moss 1982) where 60 children (aged between 1 month and 7 years 10 months at

disease) were followed-up 5-9 years later. The author reported that there was no significantly higher incidence of physical disability compared with controls.

In contrast, a prospective study undertaken in the US evaluating 79 children <16 years of age, found that 27% experienced one or more significant complication including Myocarditis, and suppurative arthritis (Edwards and Baker 1981). A further 10.1% of survivors developed late-onset arthritis or vasculitis. The study also observed that older age groups tended to be more prone to these complications than younger children were. Time since MD was not reported in this paper.

A Norwegian controlled study of 71 young male military recruits (aged 18 and 24 years of age at MD) and followed-up 3-15 years post-disease (Sander *et al.* 1984) noted that survivors anecdotally reported more general health complaints, including fatigue, than controls. It found that 13% had "relevant" complaints about their health deemed to be related to MD, whilst only 2% of controls had similar complaints. Such complaints included tinnitus, dizziness, visual disturbance, headache, irritability, and sleeplessness. The proportion of patients treated in ICU was not stated. Among the 71 survivors, 57 had had meningitis with or without septicaemia and 14 had septicaemia. The authors also reported other physical sequelae; arthritis (13%), muscle pain 7%) and chronic skin disease (4%).

Neurological sequelae have also been reported, for example, in an uncontrolled study that prospectively evaluated 93 survivors of all ages, one year after meningococcal septicaemia and meningitis. Seven out of 52 adults and 1 out of 41 children exhibited abnormalities in the neurological examination such as asymmetry of reflexes, diplopia, and unsteady gait (Naess *et al.* 1994). No other physical sequelae were assessed.

Fellick et al followed-up 115 children aged 1 month to 15 years at MD, 9-10 years later with age and sex matched controls (Fellick *et al.* 2001). They found that the majority of survivors did not have gross neurological deficits. However, when objective measures assessing motor and coordination skills were administered it was found that 16.5% of cases compared to controls had significant problems.

Hearing loss is found in MD survivors only when survivors have had meningitis with or without septicaemia – see Table 2.1.

Table 2.2 MD outcome studies reporting the prevalence of hearing loss in survivors of all ages

Study	Case sample at follow-up	Age at MD	Age at follow-up	Follow-up time	No of cases assessed for hearing problems	Rate of hearing loss %
Fellick et al, 2001	115	1 month to 15 years 3 months	8 years 9 months to 25 years	9-10 years	109	4.3
Drake et al, 2000	65	6 weeks to 15 years	Not stated	6-12 weeks	49	4.2
Moss, 1982	60	1 month to 7 years 10 months	Not stated	5-9 years	60	10
Harrison, 2001	255	<15 years to >25 years	<15 years to >25 years	Not stated	Not stated	5
Edwards et al, 1981	79	Not stated	<16 years	Not stated	Not stated	9
Erickson et al, 1998	420	<1 to >60 years	Mean 13.5 (exact range not stated)	9-72 months	420	1.9 serogroup C & 1.9 serogroup B
Naess et al, 1994	93	<2 months to >50 years	Not stated	1 year	78	16.7
Erickson et al, 2001	25	Not stated	Not stated	Not stated	25	4
Sander et al, 1984	71	18-24 years	Not stated	3-15 years	71	7
Djupesland et al, 1983	102	Not stated	Not stated	6 weeks	102	5.4
Dawson et al, 1990	35	2 months to 17 years	Not stated	Not stated	35	8.6

As Table 2.2 shows, extreme variability in the incidence of hearing loss following MD is reported in the literature reviewed. The degree of hearing loss varied from 1.9% (Erickson and De Wals 1998) to 16.7% (Naess *et al.* 1994). The variations in levels of hearing loss across studies may be in part be due to the differences in the timing of the hearing assessments following the acute stage of MD, the methods of evaluation [in some cases self-report questionnaires], age at MD, the severity of disease, follow up rates, and the size of the study sample.

2.4.2 Psychosocial outcomes

This area has been poorly studied with only three of studies reviewed exploring psychosocial outcomes in MD survivors.
Sander et al, prospectively followed-up 71 male MD survivors aged 18-24 years at disease, 3-15 years after the disease (Sander *et al.* 1984). Survivors were aged 18-24 years at disease. Sixty-four controls were recruited for comparability. The study found 29% of the young men believed their vocational choices and educational success had been affected post-MD. Unfortunately, an unvalidated questionnaire was used to collect this information, with reliance placed on the subjective experience of participants.

Other studies have focused on quality of life (QOL) post-MD. For example, in the retrospective Canadian study of over 400 MD survivors (Erickson and De Wals 1998), apart from the physical sequelae of MD which was its main focus, also examined quality of life (QOL). The study noted that 23% of 231 survivors who completed a questionnaire reported poorer QOL since MD. It found that a number of different psychosocial factors compromised QOL, including reduced energy, increased anxiety, and a reduction in leisure activities and the ability to work. An overall impairment score was calculated providing an estimate of the magnitude of reduction of QOL. Again, an unvalidated postal questionnaire that included 12 general statements concerning different aspects of QOL was used and was not specifically related to MD.

In a further uncontrolled retrospective study in the US the same authors administered the EuroQOL EQ5D quality of life questionnaire (EuroQol Group. 1990) to 25 college students and found that 20% of survivors reported a reduction in QOL post-MD, primarily in those survivors who had physical sequelae (Erickson *et al.* 2001).

2.4.3 Neuropsychological sequelae

There have been few studies on the neuropsychological sequelae following MD, and even less in relation to adolescents. In general, relatively inconsistent findings have been observed across the few studies identified for review. Methodological variations

are likely to be responsible as discussed previously. Consequently, it is difficult to draw meaningful conclusions or compare existing findings to adolescents. While major physical sequelae are simple to detect clinically, subtle neuropsychological abnormalities require a carefully selected control group for adequate comparison. Moreover, the neuropsychological sequelae of septicaemic MD has not been examined or related to possible social and functional effects. Prospective studies and adequate sex and age matched control groups are necessary for the study of subtle neuropsychological outcomes. A more complete understanding of how brain insults affects adolescents requires prospective research.

Several of the studies conducted have found minimal or no evidence of cognitive dysfunction post-MD. For example, in a matched case-control study, Moss prospectively evaluated 60 children aged one month to just under 8 years at MD (Moss 1982). Survivors were assessed 5-9 years post-disease. All survivors had a diagnosis of meningococcal meningitis. The Wechsler Intelligence Scale for children (revised) (WISC-R) and the Burt reading Test were administered by educational psychologists. Only a "tendency" towards lower performance and lower IQ was found in cases compared to conrtols which failed to reach statistical significance.

Similarly, Naess et al, prospectively assessed children and adults, including teenagers one year post-MD (n=93, [52 adults and 41 children]) (Naess *et al.* 1994). This was a controlled study with only nine participants assessed using the Halstead test battery. Only two patients were reported to have deficits (mild to severe), one of whom was a young girl of 17 years with deficits found in attention and concentration. However, the study sample is far too small for meaningful conclusions to be drawn.

In contrast, Fellick et al, in a well-conducted case-control study, examined the long-term neurodevelopmental outcomes of 115 children, aged one month to 15 years at disease, and followed prospectively for evaluation 8-10 years post-MD (Fellick *et al.* 2001). Age and sex matched controls were also recruited. Age at assessment ranged from 8 years 9 months to 25 years. Objective measures of cognitive ability were administered which included The Wechsler Intelligence Scale for Children, 3rd edition, UK (WISC-III) and the Visual Motor Integration Test to evaluate the ability to copy a sequence of geometric forms. The study found that cases obtained

significantly lower scores on psychometric tests, achieving on average 6.4 points lower in total IQ compared to controls. In addition, teachers and parents reported behavioural problems and 38 cases had special educational needs compared to 17 controls.

Only one Norwegian case-control study assessed young adults although it did not report specifically on the nature of neuropsychological disturbances. Seventy-one male survivors aged 18-24 years at MD were followed-up 3-15 years post-disease. Survivors reported problems with memory (15%), and concentration (17%), with controls reporting no such problems (Sander *et al.* 1984). However, standardised neuropsychological tests were not administered affecting the validity of the findings.

Thus far, no systematic prospective study investigating neuropsychological outcomes in adolescents has been conducted.

2.5 Findings from outcome studies on bacterial meningitis of all aetiologies

The outcomes of meningococcal meningitis have also been assessed by studies that have examined all aetiologies of bacterial meningitis. As the majority of cases of MD present as meningitis, these studies are important sources of information. However, few studies have included adequate numbers of survivors of meningococcal meningitis to form any firm conclusions or indeed compare to adolescents. Most outcome studies have concentrated on major physical and neurological impairments in children diagnosed at young ages, with the main pathogen *Haemophilus influenzae* as the primary focus (Feigin *et al.* 1976;Feldman and Michaels 1988;Grimwood *et al.* 1995;Grimwood *et al.* 1996;Sell *et al.* 1972;Sproles *et al.* 1969;Tejani *et al.* 1982).

What follows is a brief review of the main studies and again it is possible to present the findings on outcomes under three separate headings: physical, psychosocial and neuropsychological.

2.5.1 Physical sequelae

In 1993 a meta-analysis was published which examined 45 outcome reports of bacterial meningitis of all aetiologies involving 4920 children up to 19 years of age

(Baraff *et al.* 1993). The review included 19 reports of prospectively enrolled cohorts from developed countries (n=1602). Two-hundred and twenty-seven children with meningococcal meningitis were included in the analysis with 7.5% having one or more physical outcome such as deafness, mental retardation (defined as IQ less than 70), spascity or paresis and seizures. The commonest sequela was deafness with 6.4% of meningococcal meningitis suffering from some form of hearing impairment (see Table 2.3).

Generally, physical sequelae following meningococcal meningitis were reported to be less than for meningitis caused by *Haemophilus influenzae* and *Streptococcus pneumoniae.* The highest mortality rate was associated with *Streptococcus pneumoniae* (15.3%), and *Haemophilus influenzae* was associated with the lowest rate (3.8%). The mortality rate for *Neisseria meningitidis* was 7.5%.

Overall, detectable sequelae were not found in 83.6% of survivors of all causes of bacterial meningitis. Deafness was found in 10.5%, bilateral severe or profound deafness in 5.1%; mental retardation in 4.2%; spascity and /or paresis in 3.5% and seizure disorder in 4.2%.

The meta-analysis was a comprehensive review of the existing literature on all causes of bacterial meningitis. However, it is important to note that most studies focused specifically on bacterial meningitis caused by *Haemophilus influenzae*, with a large number of the studies designed to evaluate newer antibiotics. Therefore, cases may have been excluded if they presented in shock or with a high probability of death. This can be the case for patients with MD in which septicaemia may be present, and may account for the low numbers of sequelae in MD survivors.

Other works including survivors of meningococcal meningitis have indicated varying rates of sequelae with neurological abnormalities found in 4.7% of survivors (Grimwood *et al.* 2000;Taylor *et al.* 1996).

Although a single study found that a small group of children surviving meningococcal infection had no physical sequelae (Jadavji *et al.* 1986), most studies reported a risk between 8.5% (Grimwood *et al.* 1995) and 14% for major physical sequelae following

meningococcal infection (Jadavji *et al.* 1986;Pomeroy *et al.* 1990). The timing of assessment may be important as Pomeroy identified 37% with abnormalities at one month post illness, while at one year only 14% remained so (Pomeroy *et al.* 1990). Several studies have mean length of follow-up over 5 years (Grimwood *et al.* 1995;Pomeroy *et al.* 1990).

Table 2.3 Outcomes of bacterial meningitis by causative agent: meta-analysis of prospective cohort studies from developed countries (Baraff et al, 1993)

2.5.2 Psychosocial

Behavioural and social problems have been reported to be more common after meningitis in early childhood (Grimwood *et al.* 1996).

Very little research has focused on psychosocial outcomes of all causes of bacterial meningitis and that have included survivors of meningococcal meningitis. Only one study reports on this. In a prospective cohort study using age and sex matched controls Grimwood et al evaluated 158 survivors of all causes of bacterial meningitis (n=7 MD) with Hib as the major pathogen (Grimwood *et al.* 1995). Children aged between 3 months and 14 years (average 8 years) at disease were followed up 5 and 10 years later. A standardised scale was used (Teacher Report Form) which assesses social and school adjustment and a good response was achieved. Parents whose children had meningitis completed a Child Behaviour Checklist questionnaire and indicated more behaviour problems although the scores only approached significance. Teachers also rated child survivors as having more behaviour problems and reduced adaptive functioning. However, little is known about the effects of neuropsychological sequelae of meningitis on behaviour and social adjustment.

2.5.3 Neuropsychological sequelae

Previous studies of neuropsychological outcome of bacterial meningitis of all aetiologies, which have included meningococcal meningitis survivors, have predominately focused on children diagnosed at young ages. Commonly the focus of these studies has been on *Haemophilus influenzae* with *Neisseria meningitidis* included in far smaller number. However, more recently studies are emerging which have focused on adults (Hoogman *et al.* 2007).

A prospective case-control study of children under 14 years (mean age 17 months at meningitis, predominantly HiB) using standardised measures found that survivors 7 years post-disease had significantly lower IQ scores and poorer reading ability, visuo-motor co-ordination, learning, memory and executive skills than controls (Grimwood *et al.* 1995). Overall, 18.5% of the cohort had minor neurological or psychological sequelae (Grimwood *et al.* 1996). Neuropsychological assessment was performed again on 109 survivors from the original cohort, 12 years post-disease. The study found that cognitive deficits at 7 years following infection had persisted with

continuing problems in intellectual, academic and high level cognitive function. Compared to controls, survivors showed significantly lower IQ scores and poorer academic abilities on tasks requiring high level skills, including complex linguistic ability, new learning, and executive functions such as organisation, problem solving and mental flexibility (Grimwood *et al.* 2000).

Studies among adults after bacterial meningitis have described cognitive slowness, and impairment of psychomotor performance. For example, a recent Dutch study was conducted to assess cognitive outcome in 155 adults (79 after pneumococcal meningitis and 76 after meningococcal meningitis) and 72 controls (Hoogman *et al.* 2007). Survivors were aged >16 years (mean age 38.9 years) with good recovery. Controls were not randomly recruited but were mainly partners, relatives or close friends of the survivors. However, standardised measures were used to assess cognitive ability. Survivors were drawn from three prospective long-term follow-up studies and assessed post-disease. Months between disease and assessment for pneumococcal survivors were mean 54.7 ± 44.0 months and for meningococcal meningitis survivors, mean 68.8 ± 49.4. Cognitive impairment was found in 32% of survivors, which was similar for survivors of pneumococcal and meningococcal meningitis. The authors found significant differences between cases and controls. The prevalence of cognitive impairment between survivors after pneumococcal and meningococcal meningitis was similar. The study found that pneumococcal survivors had more impaired test results in memory than survivors of meningococcal meningitis.

In another study 22 adult survivors of bacterial meningitis of all causes (none with MD) were cognitively assessed (mean age 52.5 ± 17.1 years) 30 ± 11 months after disease. Psychometric tests were used and 17 controls were recruited for comparability. Cognitive speed and psychomotor performance and concentration as well as visuo-constructive capacity and memory functions were significantly impaired compared to controls. Survivors of pneumococcal meningitis had lower test results than survivors of other causes of bacterial meningitis (Merkelbach *et al.* 2000).

2.6 Possible effects of Intensive Care admission

Due to the severity and life-threatening nature of MD, ICU admission is often routine in the early stages to treat coma, shock and purpura fulminans. However, regardless of disease aetiology, studies that have examined patients admitted to ICU, have shown that long-term morbidity (physical, psychological or psychosocial) can continue post-discharge.

Only one British study has examined the effect of ICU admission on MD survivors (Judge *et al.* 2002). Twenty-nine children, aged 2-15 years at MD were followed-up from a Paediatric Intensive Care Unit (PICU) and assessed 3-12 months post discharge. An overall risk was found for child psychiatric disorder in 20% of survivors with symptoms of post-traumatic stress disorder present in 62% of children. In addition, 10% demonstrated features of a stress disorder. However, the study sample was small and a comparison group was not used. It is difficult therefore to discern whether post-traumatic symptoms resulted from MD or were simply the consequence of a severe illness or PICU admission.

Estimates of Post Traumatic Stress Disorder prevalence in critically ill adults are reported to be as high as 63% (Schelling *et al.* 2001). It may be that critical illness is uniquely stressful due to factors associated with the experience of ICU such as awareness during painful procedures, a sense of helplessness, loss of control, and an imminent threat of death (Jackson *et al.* 2007).

Brooks et al examined the physical and psychosocial outcomes of ICU admission in 238 adult patients with a variety of diagnoses 12 months post-discharge. Controls were selected randomly from the local community (Brooks *et al.* 1997). Patients were all over the age of 18 years (with an ICU stay greater than 24 hours). Only three patients with sepsis were recorded and these were excluded from analysis, as the sample size was deemed too small. Compared to controls, patients reported poor health perception, poor quality of life, more health problems and depression with reduced sexual activity and greater dependency on others. Response rates achieved were however disappointingly low and a higher than expected rate of chronic ill

health was seen amongst the control group due to possible response bias. However, these findings are consistent with other studies.

Another study examined 60 patients a year after discharge from ICU and found that nearly half were suffering some degree of anxiety, socialised less than before admission, and took part in fewer activities. Unfortunately, age groups or type of illnesses were not specified (Jones *et al.* 1994). However, these findings are consistent with those found in other studies in patients post-discharge from ICU (Cuthbertson *et al.* 2004;Patrick *et al.* 1988;Scragg *et al.* 2001;Skirrow *et al.* 2001). In contrast to the above studies, an investigation of a varied case mix of ICU patients at 3 month follow-up found a low prevalence of psychological distress (Eddleston *et al.* 2000).

Longer-term outcomes have also been examined. For example, a 3-year follow-up study of 182 patients with multiple aetiologies, reported that 23% had died within a year of discharge, and that "not a single patient was found without some particular disturbance". Sixty-percent were described as having "become a different person". Interestingly, 43% were not working 12 months after discharge. Unfortunately, no control group was used for comparison purposes, which has often been the case with studies in this area. Although the paper did not specify the age group studied, patients came from adult intensive care units (Benzer *et al.* 1983). A Norwegian report on patients 12 years after ICU reported a global reduction in quality of life in patients (Flaatten and Kvale 2001).

Neuropsychological sequelae in ICU patients post-discharge are starting to emerge. The ICU can be a stressful and noisy environment with little differentiation between night and day (Biley 1994). Patients are often sedated with psychoactive drugs during at least part of their stay, the long-term effects of which are uncertain (Broomhead and Brett 2002). Hopkins and colleagues reported that 100% of patients who had Acute Respiratory Distress Syndrome experienced cognitive impairment at hospital discharge, including problems of memory, attention and concentration. Although, they demonstrated improvements at 1 year follow-up, 30% of patients were still globally impaired and 78% were impaired in one or all of the domains assessed. The authors associated the deficits with hypoxemic episodes in the ICU (Hopkins *et al.* 1999).

It is important to remember that the majority of ICU admissions are to adult units and consist of mature adults, a significant proportion of whom may have underlying chronic physical disease. As a result, the majority of research into the outcomes of ICU admission has been conducted predominately in adults. Although the findings from this research are very useful in providing insight into the possible outcomes, they may not be generalisable to teenagers. Furthermore, the majority of outcome studies of ICU admission reviewed have not used a control group of patients who have not been admitted to ICU against which to compare outcomes. Therefore, underlying disease factors are potentially major confounders in outcome studies of ICU.

In summary, although these studies are important, apart from the study conducted in young MD survivors post-discharge from PICU, the majority were conducted with adults and therefore it is difficult to extrapolate findings to an adolescent population with low incidence of background ill health. Research on ICU admission is clearly needed on adolescent MD survivors.

2.7 Chapter summary

The research that has been conducted to date has shown that meningococcal disease leaves a proportion of survivors with some degree of physical sequelae. However, an overall assessment of the results of the outcome of MD has been hampered by the diversity of both the methods used and the populations studied with a number of studies varying widely in their methodological rigour. This was particularly true among some of the older studies where different assessment instruments were used, lengths of follow-up time, varied sample sizes, and age groups and sampling procedures were sometimes unspecified. In some studies, an appropriate control group was seldom included with conclusions being based more on clinical impressions rather than objective data. Research on MD survivors would benefit from a standardised approach sufficiently defined by standards accepted throughout the field.

Until this is accomplished, it will be difficult to compare outcomes across most studies. Some of the studies used small sample sizes which questions their validity and generalisability. Consequently, it is difficult to draw meaningful conclusions or to

compare existing findings to outcomes of MD in adolescents. Establishing reliable estimates of outcomes of MD requires follow-up of larger samples over a longer period. Nevertheless, these investigations have generated important insights into the outcomes of MD across different populations.

In particular, social, neuropsychological and psychological outcomes have not been explored in all age groups and more specifically in adolescents and we lack data on young people's qualitative experience of life after MD. The subtle emotional and psychological effects of impairments have not been explored in any age group.

Furthermore, little attention has been paid to the impact of physical and neuropsychological sequelae of MD on later social, education and vocational functioning. Existing published studies have not specifically addressed these deficits, which may affect social and employment outcomes for adolescents and young people following MD. Subtle neurological and psychological abnormalities may be missed after meningitis or septicaemia, but may significantly affect later educational and employment success and quality of life. The effects of MD on quality of life and relationships have not been fully addressed. Notably, the effects of hearing loss, both socially and psychosocially, have not been explored and more specifically the effect that this would have on the adolescent's vocational and educational aspirations. For example hearing loss in adolescence has been found to lower self-esteem, cause anxiety (English 2002), depression (Marschark 2007), social isolation (Spencer *et al.* 2000) and impact on academic achievement (Lang 2002).

Neuropsychological assessment requires a comprehensive assessment of cortical integrity such as visual and verbal processing abilities, memory, attention and concentration, which are more appropriate in adolescents and young people post-MD. Tertiary-based studies are more likely to show deficits than population-based studies, age at diagnosis, length of follow-up and age at assessment are also likely to produce differing results, making it difficult to compare results across studies as well as within studies between different age groups. As reduced IQ and severe deficits are more likely in young ages and memory/attentional problems more likely in older ages, it is difficult to draw meaningful conclusions from the existing literature and relate the findings to adolescents.

SECTION B

CHAPTER 3 – METHODS

3.1 Aims and objectives

The main aims of this study were to:

- Explore the later outcome of MD in late adolescence and more specifically, to determine prevalence of educational and employment disadvantage, social isolation, stress and depression and reduced quality of life after MD;
- Investigate the prevalence of neuropsychological deficits in IQ, multiple aspects of memory, attention, verbal and visual recognition ability and executive function after MD in late adolescence;
- Examine the physical sequelae of MD in adolescence and impact on functioning;
- Explore the significance of neuropsychological deficits resulting from MD by examining their association with educational and psychological outcomes; and
- Provide the initial part of a longer-term follow-up of the outcome of MD during late adolescence.

3.2 Study design

The main purpose of the follow-up study was to investigate educational, employment, social, psychological and physical outcomes after MD in adolescence at 18-36 months after the acute episode, in comparison to normal control adolescents.

In view of the nature of the investigation, the most appropriate study design was a matched cohort study. There are a number of advantages of the cohort design. It is useful in the study of rare diseases (Grimes and Schulz 2002b), considered to be ethically safe, participants can be matched, eligibility criteria and outcome assessments can be standardised, and it is possible to examine multiple outcome variables (Oxford Centre for Evidence-Based Medicine 2007). However, outcomes

must be defined in advance; they should be clear, specific and measurable and comparable in every way for the exposed and unexposed to avoid information bias (Grimes and Schulz 2002b).

A cohort study measures exposures in a sample of individuals (a cohort) and then follows the cohort for a period of time during which disease outcomes are monitored. In population-based cohort studies, the best strategy to avoid bias when obtaining data on outcomes is to carry out standardised data collection (Sackett 1979) as was the case in the current study.

The control group should be similar in all important respects to the exposed, with the exception of not having the exposure (Grimes and Schulz 2002b). Controls in the current study were age and sex matched and resided in the same geographical area as their matched cases.

Population-based cohort studies generally evaluate multiple hypotheses, defined a priori (Szklo M 1998), as was the case in this current study. Hypotheses regarding outcome of cases were generated following the baseline study, a case-control designed study.

3.3 Study population

3.3.1 Baseline study

MD cases and controls for the current follow-up study were drawn from a large population-based case-control study. Cases and controls were recruited from six contiguous regions of England (North Thames, South Thames, Anglia and Oxford, South West, Trent, West Midlands), representing approximately 65% of the population of England (hereafter referred to as the baseline study) (Tully *et al.* 2006).

The objectives of the baseline study were to investigate the risk and protective factors for the development of MD in adolescents during the adolescent peak (in 15-19 year olds). The baseline study was conducted between January 5th 1999 and June 9th 2000.

Incident cases were recruited through regional Consultants in Communicable Disease Control, clinicians and the national meningococcal reference unit.

Eligible participants were teenagers aged between 15 and 19 years who were admitted to hospital with a primary clinical diagnosis of meningococcal infection (signs of septicaemia or meningitis in association with hemorrhagic rash, or both). Laboratory confirmation of disease was sought at the reference laboratory in Manchester through culture or detection by polymerase chain reaction (PCR) of *Neisseria meningitidis* from a normally sterile site or serodiagnosis in a patient with a clinically compatible illness.

Cases were excluded if they were identified after the fifth day of admission to hospital, the subject had died, the attending doctor declined to participate, the subject did not speak English, or approval from the local research ethics committee had not yet been obtained.

Controls were recruited from the case patient's general practitioner's list of patients. Each general practitioner was asked to contact the three patients on their list of the same sex as, and closest date of birth to, the case. This was to control selection bias by the doctor. Controls were recruited nearest in age to the case. If none of these participants consented, the doctor was requested to send invitation letters to the next three who were nearest in age. Of the 144 controls, 55 (38%) were the first control and 36 (25%) were the second control approached. In 20% of cases, we recruited the fourth or greater control. The median age at referral for controls was 17.7.

One hundred and forty-four case control pairs (age and sex matched) were recruited for the baseline. Seventy-four cases were male (51%); median age 17.6.

3.3.2 Follow-up study

Cases and controls who consented at baseline to being contacted for follow-up (approximately 95%) were considered eligible for inclusion in the follow-up study.

The follow-up study was conducted from September 2000 until July 2002, at University College London Hospitals, 18 to 36 months after disease.

3.3.2.1 *Sample size estimation for follow-up*

Determination of the appropriate sample size is a crucial part of study design. Power calculations were conducted to estimate the sample size required at follow-up in order to examine the three hypotheses in this study to detect clinically important differences between cases and controls.

Power analysis demonstrated that 88 matched case-control pairs would be required to provide 80% power at 5% significance level for the outcomes shown in Table 3.1, thus avoiding a type I error (rejecting the null hypothesis incorrectly), or a type II error, (accepting the null hypothesis incorrectly) (Jones *et al.* 2003).

Data were derived from StatCalc using published data from previous outcome studies (major physical disability (Erickson and De Wals 1998a), neuropsychological deficit (Grimwood *et al.* 1995) and for stress using unpublished data from the Risk Factor Study (Tully *et al.* 2006). Table 3.1 refers.

Table 3.1 Estimation of sample size at follow-up

Variable	Prevalence in cases	Prevalence in controls	Number of case-control pairs required
Major physical disability	15%	<1%	71
Stress scale score greater than 4	25%	8%	69
Neuropsychological deficit	20%	5%	88

3.4 Recruitment at follow-up

I recruited participants to the follow-up study, approaching the first 115 case-control pairs on the cohort list, primarily to minimise selection bias and to correct for attrition.

Participants for follow-up were initially contacted via telephone and those who agreed to participate in the follow-up assessment were sent an appointment letter to their

home together with an information sheet outlining the aims of the study and providing a detailed explanation of what their participation would involve. The invitation letter and telephone call assured the young person that they had no obligation to participate, and that prior participation in the baseline study did not obligate them to participate in follow-up. Appointments were made for participants at a time that best suited them.

If participants were not contactable by telephone, a letter was sent to their home address inviting them to participate together with an information sheet regarding the study. If there was no response, a final letter was sent two weeks after the first, after which they were considered lost to follow-up.

We did not aim to undertake a matched analysis. As much as possible we recruited case-control pairs together. However, if the case had agreed to participate in the follow-up study but the control had declined at baseline or decided at follow-up not to participate at the last minute, it was agreed by the research team that new controls would be recruited from the case patient's general practitioner's list.

As all participants were over the age of 16 years at follow-up, consent was taken in writing from the participants only (current NHS-E guidance) and letters and telephone calls were addressed to participants directly. Written consent was obtained at assessment.

Ethical approval was obtained by the North Thames Multicentre Research Ethics Committee.

3.5 Assessment procedures

A standardised assessment protocol was developed by the research team and piloted on the first six case-control pairs on the recruitment list. Only minor modifications were made to the protocol and therefore the six case-control pairs were included in the final sample for analysis. The assessment protocol is shown in Table 3.2.

Participants who consented to follow-up underwent a 3 ½ hour confidential assessment under standardised testing procedures. Participants were offered a short break 2.5 hours into the assessment.

Table 3.2 Assessment protocol of cases and controls

Tests / Questionnaires	Duration (minutes)
Signing the consent form and describing the assessment	
Annotated Scale of Bodily Injuries (ASBIR)	10
Questionnaire for Young People	10
Rey Auditory Verbal Learning Test (RAVLT) – Trials I-VII	15
Cambridge Neuropsychological Test Automated Battery (CANTAB)	30
RAVLT Recall trial after 30 minutes delay	10
CANTAB	65
SHORT BREAK	
Rey Osterrieth Complex Figure (ROCF) test (copy subtest)	10
National Adult Reading Test	40
WAIS-R – Vocabulary subtest	
Stated Hand Preference Questionnaire	
A-FILE Questionnaire	
Clinical Outcomes in Routine Evaluation -Outcome Measure (CORE-OM)	
Chalder Fatigue Scale	
Beck Depression Inventory (BDI-II)	
Social Support Questionnaire (SSQ6)	
Quality of Life Scale	
SF-36 II Health related Quality of Life	
Rey-Osterrieth (recall subtest and recognition)	5
WAIS-R – Block Design subtest	15

I conducted all assessments on participants for the follow-up study. The study was arranged so that each control was interviewed within one day of the case wherever possible.

Participants were assessed in the study centre or at home in as quiet and distraction-free environment as possible if unable to attend the centre, University College London Hospitals. Participants were reimbursed for travel costs if they travelled to the study

centre. After completion, all participants were given a £20 CD voucher in order to thank them for their participation. The full assessment was carried out in one session.

Participants completed a battery of neuropsychological tests and questionnaires. The supervised questionnaires measured health behaviours, educational, social and vocational function, depression, social support, disability, and quality of life.

3.6 Data collection

Data were collected at 2 time points.

Time 1 (Baseline)
Baseline data were taken from the Baseline study about function/events in the 2 weeks immediately before onset of MD (for cases) or prior to interview (for controls) and forms the first data point (Time 1). Data were gathered by interview from cases and controls within 4 weeks of onset of MD in cases.

Time 2 (Follow-up)
I collected Time 2 (follow-up data) for this doctorate. Cases and controls were interviewed between 18 and 36 months after interview on the Baseline study. Participants were again asked questions about their life and function in the 2 weeks prior to interview.

3.7 Outcomes measured at baseline

A. The following information was collected in the Baseline study (Time 1) and again for Time 2 (Follow-up study). These variables were examined for differences between cases and controls and for changes between the premorbid (Time 1) and follow-up (Time 2) periods of time. Data were obtained from cases pertaining to the two-week period before admission to hospital, as specific, not necessarily habitual, behaviours were of interest.

3.7.1 Social function - Questionnaire for young people

The questions in the questionnaire focused on:

Cigarette, alcohol and other drug consumption in 2 weeks prior to interview

- Use of cigarettes (numbers per day)
- Alcohol (units per week)
- Illicit drug consumption (yes/no) in 2 weeks prior to interview.

Change between Time 1 and Time 2 was calculated.

Intimate social contacts in 2 weeks prior to interview;

- Whether the case/control had a partner. Change in the percentage of intimate relationships was assessed
- Place of residence whether dependent on parents or independent. Change in independence before and after MD was assessed.

Other social activities (within the previous 2 weeks)

- Hours per week of social contacts outside family
- Hours per week of attendance at dances and parties, clubs and raves
- Hours spent in other group social activities – church and youth groups.

School, college or work activities and environment

- Type of school/college/work and location
- Socio-economic status – vehicle and home ownership.

The following were calculated for Time 1 and Time 2

- The percentage of cases and controls in education or in employment
- Socio-economic status of controls and cases – through vehicle and home ownership.

3.7.2 Psychological measures at baseline

3.7.2.1 Personal and family life stress

The Adolescent-Family Inventory of Life Events (A-FILE) (McCubbin *et al.* 1982) was administered to cases and controls to assess stressors of family life. The A-FILE is a 50-item self-report scale of life-events and changes which the adolescent perceives his or her family to have experienced during the previous 12 months.

The A-FILE has been used extensively as a measure of stress in adolescent studies. For example, adolescents and self-harm (Tulloch *et al.* 1997), stress in adolescence (Araujo *et al.* 1999), cholesterol levels and stress in a group of adolescents (Coleman *et al.* 1998), family counselling research (Volker 1995), social support and adolescence (Carty 1989), family stress (Ravert and Martin 1997) and adolescents within at risk families (Garbarino and Schellenbach 1984).

Content

The scale is subdivided into six subscales of family life:

i) Family responsibilities: (19 items) relating to interpersonal tensions and to strains owing to health care and finances;

ii) Family changes: (14 items), that consists of items relating to role or status transitions of family members, change in role or status of a family member, the addition of family members, or geographical mobility of the family unit or a member. Transitions, also includes items such as parental separation, divorce, remarriage, parent becoming unemployed or starting a new job and child or adolescents transferring to new school.

iii) Family sexual matters: (4 items) relating to pregnancy, childbearing and the onset of sexual activity by a teenage member of the family.

iv) Family losses: (7 items) focuses on the death of a family member, other relatives or friends and to the loss of property or income.

v) Stresses at school and substance use: (4 items) relating to use of drugs or alcohol, conflict about substance use, and premature exit from school by a family member.

vi) Family legal stresses (2 items) relating to conflict with the law, the arrest or assault of a family member.

Participants were asked to respond if the event had occurred within their family and to rate the distress of an event on a standard 10 cm visual analogue scale, with 0 corresponding to no distress and 10 to extremely distressing. The distance of the mark along the line was measured as a value.

Scoring

Scores obtained: Total Stress score (range 0-50) and Total Distress score (range 0-500). Individual subscale scores can also be obtained for the number of stressful events experienced [responsibilities (range 0-19), changes (range 0-14), sexual matters (range 0-4), losses (range 0-7), stresses at school and substance abuse (range 0-4) and legal stresses (range 0-2)]. Higher total and subscale scores denote a higher number of stressful events and greater distress.

Validity and reliability

As a measure of life stressors, the A-FILE is an established psychometric instrument (McCubbin and Patterson 1983) with good construct validity and internal reliability (total scale alpha .83) (McCubbin *et al.* 1982). It has been controlled for symptom contamination, thereby eliminating confounding by health-related symptoms or by major illness.

Reliability coefficients for each subscale have been established: transitions (.52), sexual issues (.43), losses (.45), responsibilities and strain (.74), substance use issues (.66) and legal conflicts (.46) (McCubbin *et al.* 1982). Test-retest reliabilities over a 4- to 5-week period have been reported to range from .64 to .84 (McCubbin and Thompson 1991).

Variables used:

- Total Stress score (range 0-50)
- Total Distress score (range 0-500).

The change in life stress between Time 1 and Time 2 was assessed.

NB. Hospitalisation due to the acute MD event was excluded, but the hospitalisations subsequent to the initial MD hospitalisation were included.

3.7.2.2 Social support

Social support in cases and controls was assessed using the short form of the Sarason Social Support Questionnaire (SSQ6) (Sarason *et al.* 1987), a widely used measure of perceived social support in adolescence and young adults. The SSQ6 is an abbreviated instrument derived from the well-known the 27 item Social Support Questionnaire (SSQ) (Sarason *et al.* 1983).

The SSQ6 is used extensively in different research areas. For example, it was used to assess social support in patients with pulmonary disease (Sutton *et al.* 1999), gynaecological problems (Reid *et al.* 2002), epidemiological studies of idiopathic juvenile arthritis (Packham and Hall 2002) and HIV research (Prado *et al.* 2002). It has also been used in psychological research such as social support and attachment (Kafetsios and Sideridis 2006) and abuse within the family (Schaeffer *et al.* 2005).

Content

The instrument comprises six items assessing two important parts of social support for every item. Each question presents a situation and requires a two-part answer:

(i) Participants were asked to identify the people to whom they could turn to and on whom they could rely in specified sets of circumstances. A maximum of nine persons can be listed as supports for each item.

(ii) Participants were then asked to rate their level of satisfaction with the available support listed for that item. The satisfaction rating uses a six-point Likert scale ranging from "very satisfied" to "very dissatisfied."

Scoring

Scores obtained: three separate scores were calculated from the SSQ6.

i) A Total Network score derived by summing the number of people reported in each of the six items and dividing by 6 (the number of questions) (range 0-9).
ii) A Total Satisfaction score obtained by calculating the mean across all six-satisfaction ratings (range 0-6).

iii) A Total Support score obtained by combining the number of people reported for each subscale and satisfaction rating and dividing by 12 to provide a mean score (range 0-7.5).

Higher SSQ6 scores indicate a higher level of social support.

Validity and reliability

The SSQ6 is psychometrically sound demonstrating excellent internal consistency reliability coefficients .90 to .93 for both the number of supportive individuals and satisfaction with support and with an overall Cronbach's alpha = .96 (Sarason *et al.* 1987). Test retest reliability is also good (r= .85) (Sarason *et al.* 1987).

The dimensions of the SSQ6 correlate with other scales measuring anxiety, depression, loneliness, and social skills, providing evidence of construct validity (Sarason *et al.* 1987).

Variables used:

- Total Network score (range 0-9)
- A Total Satisfaction score (range, 0-6)
- A Total Support score (range 0-7.5).

The SSQ6 scores (Network, Satisfaction and Total Support score) were calculated and change in social support scores between Time 1 and Time 2 was examined.

3.8 Outcomes measured at follow-up

B. The following information was collected at Time 2 only (follow-up 18-36 months after baseline interview).

3.8.1 Physical injury and disability

Physical injury and disability was assessed in cases using an adapted version of the Annotated Scale of Bodily Injuries Regulation (ASBIR) (Commission de la Santé et de la Sécurité du Travail 1987;Erickson and De Wals 1998).

The ASBIR has been used to assess physical injury and disability in a retrospective study of outcomes of MD in all ages in Canada (Erickson and De Wals 1998) and also in a study of MD amongst college students in the United States (Erickson *et al.* 2001).

The ASBIR provides a quantitative score of physical injury and disability. The impairment score is comprehensive, taking into account anatomic and physiologic deficits, disfigurement and suffering or loss of enjoyment of life, resulting from the deficit or disfigurement. The score is expressed as a percentage of physical impairment, which increases with severity of permanent injury. Scores for different types of injuries are additive, therefore it is possible for certain individuals with multiple sequelae to have a percentage score greater than 100%.

The measure asked questions on:

- Amputation – upper or lower limbs / bilateral or unilateral, and questions on prosthesis.
- Hearing loss and degree of loss
- Vertigo
- Scarring
- Impairment in walking or standing
- Impairments in upper limbs
- Symptoms consistent with Raynaud's Disease
- Epilepsy
- Speech problems

- Loss of other function.

3.8.2 Neuropsychological measures

A comprehensive battery of neuropsychological tests was administered to assess general intellectual ability, executive function, psychomotor speed, visuospatial functioning, attention and memory in both the verbal and visual domains. The neuropsychological tests administered to cases and controls are shown in Table 3.

Tests were administered in a fixed order according to the assessment protocol. Pen-and-paper tasks were administered according to standardised instructions (Lezak 1995) and computerised tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) according to CANTAB manual protocols, on a portable PC fitted with a colour touch-sensitive screen monitor. These tests are described below.

Tests were scored according to published standardised instructions. Approximately ten percent of pen-and-paper tasks were re-scored by a second trained observer to ensure reliability. All scores were correct and no changes were required.

Table 3.3 Neuropsychological measures

*Cambridge Neuropsychological Test Automated Battery (CANTAB)
(Fray *et al.* 1997)

3.8.2.1 Intellectual ability

Intellectual ability was measured in the current study to ensure that any possible group differences between cases and controls could not be attributed to differences in intellectual ability.

Full scale Intelligence Quotient (IQ) estimates were obtained from both the National Adult Reading Test (NART) (Nelson and Willison 1991) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Short Form (Wechsler 1981). Raw scores from both the WAIS and NART were converted into a scaled score with an average full-scale IQ of 100, with a standard deviation of 15 (above and below the mean). These two tests were administered not only to estimate current IQ vs. premorbid IQ but also to track possible decline over time for future follow-up.

National Adult Reading Test (NART)

Assessment of pre-morbid intellectual functioning was obtained using the NART (Nelson and Willison 1991). Reading ability is considered relatively stable following brain injury (Crawford 1992;Kaufman 1990;O'Carroll 1995).

The NART is an oral reading test that measures vocabulary and reading ability. Participants read aloud 50 phonetically irregular words. Here the reader has to 'know' the word, rather than relying on phonology to read it correctly (e.g. 'cellist', 'gauche' and 'topiary'). Knowledge of rules facilitating correct pronunciation of phonetically irregular words must have been acquired prior to any disease onset.

Estimates of premorbid IQ are derived from the number of errors. The words are ordered in increasing difficulty and the ability to pronounce these words in the right way is considered a robust indicator for premorbid functioning.

The NART has been found to be highly correlated with overall intelligence, with WAIS-R, r =.85 (Mockler *et al.* 1996;Willshire *et al.* 1991). It also possesses high internal consistency (alpha .90) (Crawford *et al.* 1988; Crawford 1989;Nelson and Willison 1991), high test-retest reliability (alpha .98) (Crawford 1989) and inter-rater reliability coefficients between .96 and .98 (O'Carroll 1987) and is capable of

predicting a substantial proportion of variance in the IQ of a normal population (Moss and Dowd 1991).

However, NART has a number of limitations. It fails to discriminate between levels in the very superior range of intelligence (Crawford *et al.* 1988), and that it does not stretch very far below the average range (Morris *et al.* 2000). There is also the assumption of English as a first language and that it is unsuitable for those who have dyslexia and articulation problems (Watt and O'Carroll 1999).

Nevertheless, the NART has become widely used as a retrospective estimator of premorbid level of intellectual functioning in neuropsychological practice and research concerning a wide range of conditions (Taylor 1999), for example, closed head injury (Moss and Dowd 1991;Watt and O'Carroll 1999), genetic influences on cognitive function (Singer *et al.* 2006), and HIV-related deficits (Damos and Parker 1994). The NART has also been employed in numerous studies into adult neural processing capacity, in particular, cognitive reserve (Stern *et al.* 2003).

Wechsler Adult Intelligence Scale Revised (WAIS-R) Short Form

Current intellectual ability was estimated using two subtests (Vocabulary and Block Design) WAIS-R Short Form (Brooker *et al.* 1986; Sattler *et al.* 1988; Silverstein *et al.* 1982;Wechsler 1981). These two subtests are frequently used for an IQ estimate, because their estimate of IQ correlates with Full-Scale IQ (alpha .90) based on all of the subtests of the WAIS-R (Hoffman *et al.* 1988;Missar *et al.* 1994;Sattler *et al.* 1988).

The Vocabulary subtest is a test of verbal knowledge and is comprised of 42 items. Participants were asked to verbally define their understanding of increasingly difficult words to assess verbal intelligence.

The Block Design is a construction test assessing visuo-constructive ability and non-verbal reasoning. Participants were shown a series of geometric designs, and were asked to construct replicas of the designs one at a time using a set of red and white blocks. Each block has two white and two red sides, and two half-red and half-white

sides with the colours divided along the diagonal. The subject's time to complete each design was recorded.

A number of studies have used the WAIS-R (short-form) for clinical research purposes (Gooding *et al.* 1999;Harris *et al.* 1996;Kremen *et al.* 1995;Seidman *et al.* 1998).

3.8.2.2 Stated Handed Preference (SHP) Questionnaire to assess laterality

Laterality (in which certain functions such as language comprehension are localised on one side of the brain in preference to the other) has been shown to affect cognitive abilities (McManus *et al.* 1983;McManus *et al.* 1993). One example is handedness (the tendency to use one hand or the other to perform activities). Typically defined as the hand that one most often prefers to use when performing uni-manual tasks (Cavill and Bryden 2003). Assessing laterality is important when conducting group comparisons to ascertain whether there are differences, as a tendency for right-handers to perform better than left-handers on visuospatial tasks has been consistently found in previous studies (Bradshaw 1989; Levy 1972).

In this study hand preference was quantified on the basis of a questionnaire (adapted from (Crovitz and Zener 1962). It has been shown repeatedly that approximately 90% of the population shows a preference for the right hand with the other 10% preferring the left hand (Annett 1985).

Participants were asked to indicate which hand they normally used to perform each of 18 common actions, some of which are bimanual. For each action, the subject was also asked to rate the frequency of use of the two hands on a five-point scale, with a rating of one being the normal response of a strongly right-handed subject, and a rating of five, the response of a strongly left-handed subject. Total scores ranged from 18 to 90. In line with other studies utilising this measure (Isaacs *et al.* 1996;Milner 1975;Vargha-Khadem 1985) a score of less than 30 was considered to be indicative of strong right-handedness, and one over 55 of strong left-handedness.

3.8.2.3 Cambridge Neuropsychological Test Automated Battery (CANTAB)

The CANTAB assesses visual and spatial recognition memory, (Owen *et al.* 1990;Owen *et al.* 1995;Sahakian *et al.* 1988), spatial memory span (Milner 1971) spatial working memory and strategy (Owen *et al.* 1992) and attentional set-shifting (including rule learning and cognitive flexibility (Downes *et al.* 1989;Owen *et al.* 1992). All tests are based on classical experimental paradigms (Fray *et al.* 1997).

Subtests on the CANTAB are graded in difficulty, minimizing floor and ceiling effects and allowing use with a wide variety of ages and diagnoses (Fray *et al.* 1997;Luciana and Melson 1998;Robbins *et al.* 1994;Robbins *et al.* 1998).

The tests have proved sensitive to mild cognitive abnormalities in psychiatric and neurological disorders (Dolan and Park 2002;Elliott *et al.* 1995a;Elliott *et al.* 1996;Kempton *et al.* 1999;Veale *et al.* 1996).

CANTAB tasks have been extensively validated in brain injury studies (Fray *et al.* 1996) and have high test–retest reliability with studies demonstrating correlations for individual test items between .56 and .86 (Lowe & Rabbitt, 1998).

The battery includes training and screening tasks designed to assess motor skill, the ability to follow instructions, psychomotor speed and accuracy, and gross perceptual skills. These are all fundamental abilities that can influence performance on the cognitive tasks.

Previous research has found that performance on the CANTAB tests is highly correlated within the specific domains (executive, memory, and attention) (Pantelis *et al.* 1997).

The battery acknowledges that cognitive functions are both diverse and modular in the sense that they are supported by overlapping yet distinct sets of neural structures that may be differentially affected by different forms of Central Nervous System pathology.

Previous studies using CANTAB

Although this is the first report on the application of CANTAB cognitive tests in adolescents following MD, the battery has been used in a wide variety of clinical populations for example:

- *Epilepsy* (Moore *et al.* 2002)
- *Schizophrenia* (Elliott *et al.* 1995;Pantelis *et al.* 1997)
- *Depression* (Elliott *et al.* 1996;Grant *et al.* 2001;Sweeney *et al.* 2000).
- *ADHD* (Kempton *et al.* 1999)
- *Antisocial personality disorder* (Dolan and Park 2002)
- *Obsessive compulsive disorder* (Nielen and Boer 2003)
- *Chronic Fatigue Syndrome* (Capuron *et al.* 2006)
- *Parkinson's Disease* (Owen *et al.* 1992)
- *Healthy older adults* (De Luca *et al.* 2003)
- *Older adults with hypertension* (Louis *et al.* 1999)
- *Alzheimer's disease* (Dorion *et al.* 2002)
- *Dementia* (Owen *et al.* 1991;Sahakian *et al.* 1988)
- *Substance abuse problems* (Sclafani *et al.* 2002),
- *Bipolar disorder* (Sweeney *et al.* 2000)

Test administration: The tests are administered with the aid of a high-resolution touch screen monitor and data is instantly recorded with scores automatically calculated and stored on the computer. I ensured that the young person was comfortably seated when starting the CANTAB testing, at the right height and that he / she was approximately 0.5 m from the monitor as recommended by the developers. Participants were asked to respond to instructions by touching the screen with the index finger of their dominant hand. After an initial explanation and completing a simple "motor screening task" successfully (touching the centre point of flashing crosses on the screen). I controlled the computer and gave verbal instructions to the participants for each task. I presented each test in accordance with the instructions detailed in the user manual.

Auditory and visual feedback is provided by the CANTAB tasks and in addition, some tasks use the press-pad. Responses were made either by touching a particular

stimulus displayed on the screen or by operating a response pad, depending on the test. Descriptions of the tasks follow.

Memory

The following tests assess visual and spatial aspects of memory:

Delayed Matching to Sample (DMS) is a test of short-term visual recognition memory based on the delayed matching to sample paradigm used extensively in primate research (Owen *et al.* 1995;Sahakian *et al.* 1988 ;Sahakian and Owen 1992). The test takes approximately 14 minutes and is sensitive to temporal and parietal lobe dysfunction (Sweeney *et al.* 2000).

Participants are presented with a complex visual pattern in a box (the sample) and after variable periods of delay (0, 4 or 12 seconds delay) the subject is instructed to choose the pattern that had previously appeared from an array of four similar patterns. The subject must touch the pattern that exactly matches the sample. Performance was assessed according to the percentage of correct responses participants selected for all delays and response latency for all delays (msec).

Pattern & Spatial Recognition Memory (SRM & PRM): these two tasks assess encoding, retrieval and recognition ability of pattern and spatial memory. They were designed by Sahakian and colleagues (Sahakian *et al.* 1988) and are sensitive to working memory impairment and therefore to frontal lobe function (Owen *et al.* 1995). The tests each take approximately 5 minutes to complete.

In the spatial recognition test, five squares are shown in different locations on the screen. Following a delay of 5 seconds, the squares are re-presented in different locations on the screen and the participants are asked to touch the location at which they had seen a square appear (the recognition stage) one of which is in a place previously seen in the presentation phase. Locations are tested in the reverse of the presentation order. This procedure is repeated a further three times each time with five new locations.

In the pattern recognition task, participants were presented with a series of 12 abstract coloured patterns appearing one after the other, and were asked to remember them. These patterns are designed so that they cannot easily be given verbal labels. Following a delay of 5 seconds, the 12 patterns were re-presented in reverse order, paired with a new pattern, and participants were asked to touch the pattern they had seen previously. This cycle was repeated with another set of 12 patterns followed by a recognition phase.

Performance on both tests was assessed according to the percentage of correct responses.

Paired Associate Learning (PAL): assesses visual memory and new learning (ability to form visuo-spatial associations). The test was designed by Sahakian and colleagues (Sahakian *et al.* 1988) and is sensitive to temporal and parietal lobe dysfunction (Jakala *et al.* 1999; Sweeney *et al.* 2000). The test takes approximately 11 minutes to complete.

The task consists of correctly locating the number of patterns presented on the screen after their first appearances. Boxes appear on the screen and each opens in randomised order. One or more of them will contain a pattern. The patterns are then displayed in the middle of the screen, one at a time. The subject is then required to remember the patterns associated with different locations on the screen and touching the box where the pattern was originally located. If the subject makes an error, the patterns are re-presented to remind the subject of their locations. The difficulty level increases throughout the test with the number of patterns increasing from one to eight. Performance was assessed by the percentage of all stages completed successfully and the total number of errors made (when the subject selects a box that does not contain target stimulus) summed across the eight stages (adjusted for the number of stages completed).

Attention

The following tests measure different aspects of attention and reaction time:

Rapid Visual Processing (RVP): test assesses visual sustained attention, although it also requires both selective attention and working memory for its successful execution (Sahakian *et al.* 1988). The test is sensitive to dysfunction in the parietal and frontal lobe areas of the brain (Coull *et al.* 1996) and takes approximately 7 minutes to complete.

RVP uses the press pad exclusively as an input device. A white box was presented in the centre of the computer screen inside which digits from 2 to 9 appeared in a random order at a rate of 100 digits per min. Participants were asked to detect three sequences of digits (i.e., 2–4–6, 3–5–7, and 4–6–8) and to register responses using the press pad. These three digit strings were shown continuously at the right of the screen to help remind participants of these target sequences. Participants responded by pressing the pad when the last digit of a target sequence was displayed. During the test, a target sequence was presented 27 times.

Afterwards, 2 sensitivity measures 'A' and 'B' were calculated using Signal Detection Theory (Green and Swets 1966;Swets 1964). The sensitivity to target sequences is reflected by 'A' and 'B' is the tendency to respond regardless of the presence of a target sequence. Both measures are based on the proportion of hits (correct responses) and the proportion of false alarms (responses made when no target sequence was presented) of the responses made during the test.

Performance was assessed by how good the subject was at detecting target sequences (RVP A) and whether there was a tendency to respond regardless of whether the target sequence was present (RVP B) and latency to respond to correct detections (in msec).

Simultaneous Matching to Sample (MTS): assesses the ability to recognise complex visual designs. This is a matching test, with a speed/accuracy trade-off. It was designed by Downes and colleagues (Downes *et al.* 1989) and is sensitive to temporal and parietal lobe dysfunction (Sweeney *et al.* 2000). The duration of the test is approximately 9 minutes.

The participant is shown a complex visual pattern (the sample) in the middle of the screen, and then, after a brief delay, a varying number of similar patterns are shown in

a circle of boxes around the periphery of the screen, that have elements in common with the target. Only one of these boxes matches the pattern in the centre of the screen, and the subject must indicate which it is by touching it.

In addition to touching the sensitive screen, participants also used a press-pad, which they were asked to hold down and when ready to make a response, to release the pad and touch the correct pattern. Performance was assessed according to the percentage of correct selections and the latency time from releasing the press pad to choosing the correct pattern on the screen.

Executive function

These tests address executive function, working memory, and planning; all associated with the frontal area of the brain.

Intra-Extra Dimensional Set Shift (IED): This is a test of rule acquisition and reversal (attentional set-shifting ability), examining the subject's ability to attend to the specific attributes of compound stimuli, and to shift that attention to a novel visual stimuli. The test was designed by Downes and colleagues (Downes *et al.* 1989) and is comparable to the Wisconsin Card Sorting Task (Berg 1948). The test is sensitive to frontostriatal dysfunction (Sweeney *et al.* 2000) and lasts approximately 7 minutes.

The task involved nine stages, with participants proceeding to the next stage when a criterion of six consecutive correct responses had been attained. The subject starts by seeing two simple colour-filled shapes, and must learn which one is correct by touching it. Feedback teaches the subject which stimulus is correct, and after six correct responses, the stimuli and/or rules are changed. These shifts are initially intra-dimensional (e.g. colour filled shapes remain the only relevant dimension), then later extra-dimensional (white lines become the only relevant dimension). Simple stimuli are made up of just one of these dimensions, whereas compound stimuli are made up of both, namely white lines overlying colour-filled shapes.

Participants progress through the test by satisfying a set criterion of learning at each stage (6 consecutive correct responses). If at any stage the subject fails to reach this criterion after 50 trials, the test terminates.

Performance was examined according to the total number of stages completed successfully, the total numbers of errors made in completing those stages (adjusted to account for participants who did not successfully complete the task) and the total number of trials to complete the task. In addition, the number of errors made prior and during the extra-dimensional shift stage (important attentional shift stage) of the task were assessed.

Spatial Working Memory (SWM): This test is a self-ordered searching task assessing the subject's ability to retain spatial information and to manipulate remembered items in working memory. The test was designed by Owen and colleagues (Owen *et al.* 1990) and is sensitive to frontostriatal dysfunction (Sweeney *et al.* 2000). The test requires approximately 8 minutes to complete.

In this task, participants are required to search through a spatial array of coloured boxes presented on the screen by touching each one in order to find blue tokens, which are hidden inside. In each trial, only a single blue token is hidden inside one of the boxes. The subject must touch each box in turn using a process of elimination until one opens with the token (a search). Once found, the next token is hidden and a new search begins. The main aim is that once a token is found within a particular box, that box would not be used again to hide a token. In the conduct of this test are four trials with each number of boxes gradually increasing until it is necessary to search a total of eight boxes. The colour and position of the boxes are changed from trial to trial to discourage the use of stereotyped search strategies. On each trial, the subject is required to try to locate all the hidden tokens and transfer them to the right side of the screen without opening a box that has been previously selected. Returning to an empty box already sampled on a search is an error ("between" search-errors).

Performance was measured by the number of *between search errors* calculated for trials of four or more tokens only. In addition, the subject's ability to adopt a systematic searching approach (*strategy score)* was measured by counting the number of times the subject begins a new search with the same box. An efficient strategy for completing the task is to follow a predetermined sequence by beginning with a specific box and then, once a token has been found, to return to that box to start the new search sequence (Owen *et al.* 1995), such a strategy results in a low strategy score.

Stockings of Cambridge (SOC): This test assesses the subject's ability to engage in spatial problem solving and reasoning. This is a computerised version of the 'Tower of London' test devised by (Shallice 1982) and adapted by Owen and colleagues (Owen *et al.* 1990). It makes substantial demands on executive function and therefore is sensitive to frontostriatal dysfunction (Sweeney *et al.* 2000). The duration of this test is approximately 8 minutes.

The subject is shown two displays containing three coloured balls. The displays are presented in such a way that they can easily be perceived as stacks of coloured balls held in socks suspended from a beam. The subject must use the balls in the bottom half of the screen to match the arrangement on the top of the screen. The balls may be moved one at a time by touching the required ball, then touching the position to which it should be moved. The time taken to complete the pattern and the number of moves required are taken as measures of the subject's planning ability. The main feature of this task is that it is possible for the subject to solve the problem in advance of making a response.

Performance was assessed on the number of problems solved correctly within the minimum number of moves (perfect solutions). In addition, initial and subsequent thinking latencies (time taken to initiate the first move, select the subsequent ball and to complete the problem for each test trial) for five moves (the most difficult level) during the trials were recorded providing estimates of cognitive speed.

Spatial Span Test (SSP): This test assesses working memory capacity. It is a computerized version of Corsi Block Tapping test (Milner 1971), and was adapted by Owen and colleagues (Owen *et al.* 1990). The test is sensitive to temporal and parietal lobe dysfunction (Sweeney *et al.* 2000) and takes approximately 8 minutes to complete.

A series of white boxes are shown on the screen. Some of the squares change in colour, one by one, in a variable sequence. At the end of each sequence, a tone indicates that the subject should touch each of the boxes coloured by the computer in the same order as they were originally presented. The number of squares range from 2 to 9 squares.

Performance was assessed by the span length, denoted by the longest sequence of boxes successfully recalled.

Psychomotor speed

The Five Stage Reaction Time task (RT): The task assesses psychomotor speed and coordination. The reaction time (simple or choice, unpredictable) to a visual target is measured (Eagger *et al.* 1991). This test is sensitive to frontostriatal dysfunction (Chari *et al.* 1996) and takes approximately 5 minutes to complete.

The task is divided into five components, the first three components are for practice purposes only, and tasks 4 and 5 are test trials. The test requires that the subject must sometimes respond by using the press-pad, sometimes by touching the screen, and sometimes both. Participants were required to lift their dominant hand from a response pad and touch a yellow spot immediately after it appears in the centre of the screen as quickly as possible. The Five choice reaction time test showed the subject five circles and the yellow spot appearing in any one of the circles. The response time to a yellow spot appearing in one of the five circles was measured.

Performance was assessed by the latency of responses consisting of two measures, the time taken to lift the dominant hand from the response pad for 5 choices (reaction time) and the time taken to move the hand from the response pad to the computer screen for 5 choices (movement time) in milliseconds.

3.8.2.4 Other neuropsychological tests administered at Time 2

Rey-Osterrieth Complex Figure Test

The Rey-Osterrieth Complex Figure Test (ROCF) is a measure of visuospatial constructional ability and complex long-term visual memory. The test was originally developed by (Osterrieth 1944;Rey 1941) and translated into English by (Taylor 1959) and is commonly used by clinical neuropsychologists with populations of all ages. High inter-rater reliability has been demonstrated on the ROCF (alpha .95-.98) (Bennett-Levy 1984a;Berry *et al.* 1991). Test-retest reliability was found to be in the .60 to .76 range (Berry *et al.* 1991;Delaney *et al.* 1988).

A number of studies have utilised the ROCF to examine the impact of severe and mild brain injury on cortical and sub-cortical integrity (Benayoun *et al.* 1969; Bennett-Levy 1984b;Brooks 1972;Leininger *et al.* 1991). The ROCF has been found to be sensitive to laterality of cerebral lesion especially when the right hemisphere is affected (Loring *et al.* 1988).

The ROCF is composed of two parts, the first requires the participant to carefully *copy* a complex geometric figure with a pencil on paper (this assesses visuospatial constructional ability), while the second asks him / her to reproduce the figure from memory, without forewarning. The *recall* part of the test assesses the participant's capacity to encode complex visuospatial information into memory and retrieval ability. In the current study, participants were asked to recall the figure, after a 40-minute delay. Instructions to participants in this current study were standardised.

In this study the most commonly used scoring procedure was used and developed by (Osterrieth 1944) and modified by (Taylor 1959). The figure contains 18 elements including crosses, squares, triangles and a circle arranged around a central rectangle.

For scoring purposes, the diagram is divided up into 18 scoring units (0.5 -2.0 points are awarded for each element) based on the accuracy of the reproduction (*copy score*). Points are based on placement and presence of distortion for each of the 18 elements of the figure. A maximum score of 2 points, one for accuracy and one for placement, is allocated to each scoring unit so that the highest possible number of points is 36. The absolute size of the drawing is not important, but the relative proportion of elements to the overall figure must be maintained. The Osterrieth scoring system treats all 18 units equally, be they isolated details or organising structures. A time limit is not imposed for the copy or recall trial although time to complete the task was recorded.

After recalling the figure the *Recognition memory subtest* was administered (Meyers and Lange 1994) to each subject. Participants were presented with internal details from the ROCF comprising of 12 parts of the two dimensional line drawing presented in their proper size, shape and orientation, mixed randomly with 12 distracters. These 24 figures were then randomly placed on 4 pages in roughly 2 columns per page,

depending on the shape and size of the figures. Participants were asked to encircle each figure that belongs to the "whole design" just drawn.

Performance was assessed using the following scores: Copy score, Recall score and the Recognition subtest score.

Rey Auditory Verbal Learning Test

The Rey Auditory Verbal Learning Test (RAVLT) was developed by André Rey in France (Rey 1941;Rey 1964) and translated into English by (Taylor 1959). The RAVLT provides measures of immediate memory, efficiency of verbal learning, effects of interference, and recall following short and long delay periods (Rey 1964;Spreen and Strauss 1998). The scores obtained from the RAVLT are frequently used in the literature to reflect different aspects of episodic memory (Blachstein 1997).

The RAVLT has consistently been ranked as one of the most popular measures utilised in neuropsychological assessment because it is brief, straightforward, easy to understand, and shown to be sensitive to brain injury (Lezak 1995). The learning measures have been found to correlate significantly, mostly in the .50 to .65 range with other learning measures (Macartney-Filgate and Vriezen 1988). Test-retest reliability correlation coefficients have been found to be .38 -.70 (Snow *et al.* 1988).

The RAVLT is appropriate for use in children, adolescents, and adults and as such has been utilised in a variety of clinical samples representing different medical and psychiatric conditions. For example, some of the more recent studies utilising the RAVLT include children with diabetes (Northam *et al.* 2001), genetic disorders (Jarrold *et al.* 2004), schizophrenia (Torres *et al.* 2001;Torres *et al.* 2004), epilepsy (Andelman *et al.* 2006), and traumatic brain injury (Masanic *et al.* 2001).

The RAVLT takes approximately 10 to 15 minutes to administer and consists of eight trials.

The standard format starts with a list of 15 common nouns (List A), which is read aloud at the rate of one word per second. The subject's task is to repeat all the words he or she can remember, in any order. This first trial (I) is a measure of immediate

memory span. This procedure is carried out five times. These first five trials (I to V) are termed the learning trials.

After Trial V, a second list of words (List B – Trial VI) a distractor list is presented, allowing the subject only one attempt at recall. The degree to which old learning can interfere with new learning is assessed in this trial (proactive interference). Immediately following this (Trial VII) the individual is asked to remember as many words as possible from the first list (List A). The degree to which new learning interferes with the recall of old information is assessed by performance in this trial (retroactive interference).

After a 30-minute delay (which were not filled with other verbal memory tests) Trial VIII was administered and the participants were asked to recall the first list of words (List A) again.

The following measures were obtained:

- Trial I: Immediate memory recall
- Trials I-V level of learning ability (sum of words recalled over 5 trials)
- Trial VI a measure of interference / proactive interference – discrepancy between Trial I & Trial VI reflects the detrimental influence of the other four learning trials and the vulnerability to interference.
- Trial VII I delay recall

3.8.3 Psychological measures at Time 2

3.8.3.1 Fatigue scale

Daily fatigue and energy levels in cases and controls were assessed using the Fatigue Scale (Chalder *et al.* 1993), an 11 item self-report scale covering the physical and mental aspects of fatigue, with higher scores denoting greater level of fatigue. This scale was originally used in a hospital-based case control study (Wessely and Powell 1998) and in a study designed to measure response to treatment (Butler *et al.* 1991). Since then it has been used in numerous epidemiological studies to assess fatigue levels in different populations (De Vries *et al.* 2003; Hotopf *et al.* 1996; Hotopf *et al.*

2003; Loge *et al.* 1998; Pawlikowska *et al.* 1994; Taylor *et al.* 2002; Wallman *et al.* 2004).

Content

Participants were asked to rate the extent to which fatigue has caused problems for them in relation to exemplar statements. *Physical fatigue* questions ask about problems with tiredness, need to rest, problems with starting things, lack of energy, decreased strength in muscles, feeling sleepy, and feeling weak. *Mental fatigue* questions asked about problems in thinking clearly, poorer memory, making more slips-of-the-tongue and difficulty in concentrating. There are 4 possible answers to each of the 11 questions with response options ranging from better than usual to much worse than usual on a Likert format.

Scoring

The scale was scored according to the continuous scoring procedure, with codes ranging from 0 to 3 and total score ranging from 0 to 33 (with higher scores signifying greater fatigue).

Scores obtained:

Total fatigue score (sum of all 11 items)

Mental fatigue score describing cognitive difficulties (sum of items 1-7)

Physical fatigue score (sum of items 8-11)

Higher scores indicate greater fatigue

Validity and reliability

The scale has been found to be reliable (Cronbach's alpha for all items 0.88- 0.90) and valid (sensitivity 75.5 and specificity 74.5) with good face validity and discriminant validity (area under the ROC curve =0.85) (Chalder *et al.* 1993), and has shown sensitivity to treatment changes (Deale *et al.* 1997).

3.8.3.2 Beck Depression Inventory (BDI-II)

The Beck Depression Inventory (BDI) was developed in the 1960s (Beck *et al.* 1961), and revised in 1996 to comply with the DSM-IV criteria for depression (Beck *et al.* 1996) as the Beck Depression Inventory-Second Edition (BDI-II). It has become the

gold-standard instrument designed to assess the intensity of depression in older adolescents and young adults and is used primarily as a screening tool in clinical and non-clinical populations (Beck 1987;Bennett *et al.* 1997). Items of the scale were derived from clinical observations of depressed patients including their typical attitudes and symptoms.

The strengths of the BDI-II is that it is brief, easy to administer, and applicable to a wide range of populations. It is the most widely used measure of depression in clinical practice and in research projects (Beck *et al.* 1988). It is not meant to serve as an instrument of diagnosis, but rather to identify the presence and severity of symptoms consistent with the criteria of the DSM-IV.

There are two main reasons why this instrument was administered in the current study. Firstly, major life events such as MD and its possible sequelae are a significant risk factor for subsequent depression and secondly, depressive symptoms have consistently been found to affect cognitive functioning (Cassens *et al.* 1990;Veiel 1997). Even in neurologically intact younger persons, depressive symptomatology may interfere with the normal expression of their cognitive abilities (Walsh 1985).

The BDI takes approximately 10-15 minutes to complete. Participants are asked to consider each statement as it relates to the way they have felt for the past two weeks.

Content

The BDI-II is a self-administered measure, consisting of 21 symptom-attitude categories or items assessing the cognitive, behavioural, affective and somatic components of depression (mood, pessimism, sense of failure, lack of satisfaction, guilt feelings, sense of punishment, self-dislike, self-accusation, suicidal wishes, crying, irritability, social withdrawal, indecisiveness, distortion of body image, work inhibition, sleep disturbance, fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido).

Scoring

Each item has one numerical answer ranging from 0 (low depression) to 3 (maximum depression) to show increasing depressive symptomatology. A total score was obtained by summing the rating for items ranging from 0-63.

Cut-off score guidelines for the BDI-II are given with the recommendation that thresholds be adjusted based on the characteristics of the sample, and the purpose for use of the BDI-II.

Scores range from low (denoting minimal depression) to high (denoting severe depression). A score of 0-13 is considered in the minimal range, 14-19 is mild, 20-28 is moderate, and 29-63 is severe. Scores of >13 indicate depressive symptomatology within the clinical range.

Validity and reliability

The BDI-II has good psychometric properties and has been shown to be a valid measure for detecting depression among adolescents (Bennett *et al.* 1997).

There are many studies supporting the validity of the BDI. The items of the BDI-II are clinically derived and have undergone extensive reliability and validation studies (Beck *et al.* 1996;Whisman *et al.* 2000). It has excellent construct validity. In fact, researchers evaluate the validity of new scales based on the BDI. Correlations of between 0.66 and 0,75 were achieved against other depression and personality scales (Beck 1970).

Internal consistency assessments of reliability have been high (>.90) in most evaluations. Beck and colleagues measured the psychometric properties of the BDI-II with samples from four different psychiatric outpatient clinics (n = 500) and one college student group (n = 120). Alpha reliability was .92 for the outpatients and .93 for the college students (Beck *et al.* 1996). Reported alpha coefficients with different undergraduate samples include .89 (Steer and Clark 1997), .90 (Osman *et al.* 1997), .91 (Dozois *et al.* 1998), .92 (Steer *et al.* 1997), .92 (Steer *et al.* 1998).

3.8.3.3 General psychological functioning

The Clinical Outcomes in Routine Evaluation-Outcome Measure (CORE-OM) (Barkham *et al.* 1998;Barkham *et al.* 2001;Evans *et al.* 2002) is an acceptable, standardised outcome measure designed to measure emotional disturbance and general psychological functioning. The measure is primarily used in service settings across multiple disciplines that offer psychological interventions in primary and secondary care (Barkham *et al.* 2005;Evans *et al.* 2002).

Content

The CORE-OM is a standardised assessment measure consisting of 34 simply worded questions all answered on the same five-point scale. The questions refer to the subject's state of mind over the preceding week. It contains 3 domains: subjective well-being, symptoms, and functioning. In addition, a measure of self-risk or harm is included. Half of the items focus on low-intensity problems (e.g. 'I feel anxious/nervous') and half focus on high-intensity problems (e.g. I feel panic/terror').

The CORE-OM taps the domains of subjective well-being (4 items), symptoms (12 items), functioning (12 items) and risk (6 items; 4 'risk to self' items and 2 'risk to others' items). Within the symptom domain 'item clusters' address anxiety (4 items), depression (4 items), physical problems (2 items) and trauma (2 items). The functioning domain 'item clusters' address general functioning (4 items), close relationships (4 items) and social relationships (4 items).

Scoring

Each item is scored on a 5-point scale ranging from 0 (not at all) to 4 (most or all of the time). The minimum score that can be achieved is 0 and the maximum 136. A total score is calculated by adding the response values of all 34 items. The measure is problem scored, that is, the higher the score the more problems the individual is reporting and/or the more distressed they are. The final result usually presented is an average per item (0-4). The score can be subdivided into those for well-being, functioning, risk and other problems.

Validity and reliability

The CORE-OM provides good internal reliability, with alphas ranging from 0.70 and 0.97 in studies with large samples (non-clinical and clinical samples) from primary and secondary care-based psychological therapy services (Barkham *et al.* 2005;Evans *et al.* 2002).

Convergent validation against a battery of existing measures such as the BDI-II has also shown to be good (Evans *et al.* 2002).

3.8.3.4 Health related quality of life

Health related quality of life was assessed using 2 self-report questionnaires that assessed different aspects of participants' personal and social function and quality of life. No adequate scales cover the age range 15 to 19 years, so one validated adult-oriented scale was used and a simple adolescent-oriented set of questions were formulated.

3.8.3.5 SF36-II

The Short Form 36 Health Survey was originally developed in the USA in the early 1990s (Ware and Sherbourne 1992) and modified to make it acceptable in the British context (Brazier *et al.* 1992).

The UK SF36 Version II (Jenkinson *et al.* 1999) was used in this current study to measure health related quality of life *(HRQOL)*. It is an extensively researched, self-report measure and the most commonly used health status measure in the world today (Staquet *et al.* 1998). It has been studied in a wide variety of populations by Ware and colleagues (Ware and Sherbourne 1992) and generates a profile of HRQoL outcomes.

Content

The SF-36 consists of 36 items, which measure eight dimensions of health: physical functioning (10), social functioning (2), and role limitations due to physical problems (4) role limitations due to emotional problems (3), mental health (5), energy/vitality

(4), pain (2) and general health perception (5). There is a further single unscaled item asking respondents about their perceptions of health changes over the past year.

Scoring

The UK SF36-II scoring system (Jenkinson *et al.* 1996) was used to calculate a score within a dimension which had a possible range from 0 (worst possible health state) to 100 (best possible health state). The subscales are not summed together to produce an overall score, instead the scores for each of the eight domains are reported.

Two summary measures were also calculated (Ware *et al* 1994;Ware *et al.* 1995); the Physical Component Summary Score (PCS) and the Mental Component Summary Score (MCS) according to algorithms specified by the developers (Ware *et al* 1994;Ware *et al.* 1995). This has the advantage of enabling a reduction in the number of statistical comparisons conducted. The component scores were obtained by aggregating the scores across the eight SF-36 subscales, and then transforming them to *z*-scores and multiplying by their respective factor score coefficients. The scores were then standardized as *t* scores with a mean of 50 and a standard deviation (SD) of 10.

Validity and reliability

The SF36-II is a reliable and valid generic measure for use among both disease and general populations. Good construct validity has been found in terms of distinguishing between groups with expected health differences (Brazier *et al.* 1992). Strong correlations were reported between the mental-health subscale and other psychological subscales (the range was r=0.51 to r=0.82) (Ware *et al.* 1993).
In the UK considerable evidence was found for the reliability of the SF-36 (Cronbach's alpha greater than 0.85, reliability coefficient greater than 0.75 for all dimensions (except social functioning) (Brazier *et al.* 1992).

3.8.4 Global quality of life

A set of simple global questions were developed about QOL. Participants were asked to rate their current global quality of life (QOL) compared to their peers, and whether they thought, their QOL had changed since the time of the baseline study. Participants

were asked to place a mark anywhere along a line between two extremes at either end (Likert Scale). The distance of the mark along the line was measured as a numeric value. Scores range from -5 to +5 with higher scores indicating better QOL.

Cases were also asked which of areas of their life (home, friendships, academic and vocational achievements, leisure activities, and physical ability) had been most affected by MD. Choices of response ranged from 'Not at all' to 'A great deal'.

3.8.5 Social and vocational domains at Time 2

Variables used:

- *Educational / employment attendance.* The number of days missed from education or work in the 3-month period before interview was noted.
- *Educational achievement level.* Those participants in education were asked to rate their level of achievement during the school or college year after MD on a simple scale of high, average or low achievement. Participants were also asked regarding the results of most recent exams.
- *Educational Outcomes:* participants reported the number of exam passes obtained at GCSE (General Certificates of Secondary Education) level and A (Advanced) Level, and whether they had failed any exams in the year before interview.

3.8.5.1 Disease variables from Time 1

The following information was gathered from Time 1 and was used in the analysis in this study to examine the association of disease and demographic characteristics at baseline (Time 1) with outcomes at follow-up (Time 2)

- ***Severity of illness*** – indicated by admission to an intensive care unit (ICU) and length of stay in ICU
- ***Meningococcal serotype*** (B, C) or other (Y, W135, or ungroupable)
- ***Clinical definition of type of MD*** - (meningitis only, septicaemia only, or mixed disease). This was defined at baseline in cases with a clinical diagnosis of meningococcal infection (signs of septicaemia or meningitis in association with haemorrhagic rash, or both). Laboratory confirmation of disease was also sought

through culture or detection by polymerase chain reaction of *Neisseria meningitidis* from a normally sterile site or a serodiagnosis in a patient with a clinically compatible illness.

3.8.6 Follow-up of cases

Cases were asked at interview whether they had been seen by any health professional after discharge from hospital since MD.

3.9 Data analysis

The aim of the follow-up study was to determine the outcomes in a cohort of adolescents who had MD between 15 and 19 years of age by making comparisons with a group of adolescents of the same age and sex who did not have MD.

Data from this study were used to test the hypotheses that educational, vocational, social and psychological function, quality of life and cognitive function were poorer in survivors of adolescent MD than in controls.

As many of the outcomes under study are significantly influenced by age and gender, differences between cases and controls were assessed using linear regression controlling for age, gender and time since baseline.

3.9.1 Cross-sectional analyses

3.9.1.1 Group comparisons

Descriptive statistics were computed for cases and controls to compare results of measures and to identify specific variables that would serve as predictors of poor outcome at follow-up in regression models.

All quantitative variables were initially assessed for approximate normal distribution. Variables following a normal distribution are summarised by mean and SD.

Independent t-tests were used to compare the difference in mean values between cases and controls to examine differences between the two groups for continuous variables.

Quantitative variables having non-normal distribution were summarised by median and range. The Wilcoxon-Mann-Whitney test was used to compare the difference in median values for cases and controls.

Fisher's exact test was used to compare proportions and distributions between the two groups for categorical variables.

All analyses were two tailed, and statistical significance was defined at the 0.05 level.

3.9.1.2 Cases only

A series of analyses were conducted in cases only.

Neuropsychological variables:

i) *To examine the effect of age at baseline and gender on neuropsychological scores:* Analyses of covariance (ANCOVA) were performed to examine the effect of gender and age at baseline (independent variables) on scores of neuropsychological measures (dependent variables) in cases only. The variable of gender by age at baseline (that is, the interaction term), was also added to the models.

ii) *To assess if male and female MD survivors were differentially affected by the age at which they contract MD* – Regression analyses were computed to confirm the results from the ANCOVA and to take full advantage of all the variance in the age at baseline and gender variables. Each regression model included scores from the neuropsychological measures as dependent variables with gender and age at baseline again used as independent variables. In addition, the interaction term (gender and age at baseline) was included in linear regression models.

iii) *To explore the association of mental health functioning with performance on cognitive tests.* This was examined using linear regression. Cognitive test scores for cases were converted to *z*-scores using the mean and standard deviation of the control

group for each individual test to explore the contribution of mental health functioning to neuropsychological test performance. Scores for the Beck Depression Inventory and the SF36 Mental Health Summary score were regressed against each of the cognitive domain z-scores in linear regression, adjusting for age at testing and gender.

iv) *The association of premorbid IQ (NART score) with cognitive deficit and educational achievement* was examined using linear regression, adjusting for age at testing and sex. NART scores were categorised into cases that achieved <100 (below average) vs. >=100 (average and above) and further sub-divided to <115 vs. >=115 and regressed against a cognitive summary score (CSS) and educational variables (number of passes at GCSE and A level). The rationale for the CSS is described in the cross-sectional results section of this thesis.

Identified deficits on functioning

i) *The association of identified deficits on functioning*: The ASBIR score and the cognitive summary score(CSS) were entered into multiple linear regression models as independent variables with educational achievement (number of passes at GCSE and A level), mental health functioning (BDI-II and SF36 MCS), QOL, fatigue (Total Fatigue Score) and social support (SSQ6 Total score) as the dependent variables, adjusting for age at follow-up and gender.

ii) *The relationship of mental health function and social support*: Regression analyses were conducted with mental health scores (BDI-II and SF36 Mental Component Score) with the SSQ6 total social support score, adjusting for age at testing and gender.

iii) *To examine the association of MD with depression* a series of logistic regression analyses of depressive symptoms (BDI score >13) were regressed onto variables known to be risk factors for depression, including life stress, female gender and age, and socioeconomic status (SES). Initially, the regression model was unadjusted for age at follow-up, then partially adjusted, then in an "all in" multivariate model. Life stress is a major determinant of depression (Brown and Harris 1978).

3.9.2 Longitudinal analyses

These were undertaken in cases only to assess:

i) *The association of disease and demographic characteristics at baseline* with physical disability, mental health, fatigue, and cognitive deficit were examined using linear regression adjusted for age at disease and gender. Disease-related factors examined included MD seroGroup (C compared with B), type of MD (septicaemia or mixed septicaemia / meningitis compared with meningitis alone), severity of disease (number of days spent in Intensive Care Unit), age at MD and gender. Predictors (disease-related variables) were chosen based on findings from previous studies on outcomes of MD known to be associated with poor outcome in survivors (Erickson and De Wals 1998; Erickson *et al.* 2001).

ii) *The association of follow-up after MD* with disease severity (ICU admission), physical disability, social support, quality of life and mental health functioning using linear regression of follow-up post-MD on physical disability, social support, quality of life and mental health functioning.

iii) *To assess if cases and controls changed differently at follow-up in terms of stress, social support and health behaviours* from baseline a series of linear regression analyses were performed. Status, gender and age at follow-up with social support and stress scores at follow-up were entered into the model, adjusting for scores of social support and stress at baseline.

Stata 8 statistical software was used for data analysis.

All computer data were stored under the terms of the Data Protection Act.

3.10 The researcher's role within the follow-up study

The follow-up study was a collaborative study between 3 clinicians, one a professor of paediatric epidemiology, one a consultant of adolescent medicine, and one a consultant clinical psychologist, together with a statistician.

It is important to clarify my role within the study.

The design of the follow-up study, writing of the grant application for support to carry out the study, and obtaining ethical approval were complete before I was appointed to undertake the study. Therefore, I had no input into these areas.

As the sole study researcher, I was involved in designing the assessment protocol and questionnaires, sourcing measures used to assess outcomes, tracing and recruiting young people, and conducting all participants' assessments. I was also responsible for the day-to-day administration of the study, including contacting GPs and as well as designing databases, coding and data entry. I undertook all analysis of the data with guidance from a statistician.

SECTION C

CHAPTER 4 – RESULTS: CROSS-SECTIONAL ANALYSES

4.1 Introduction

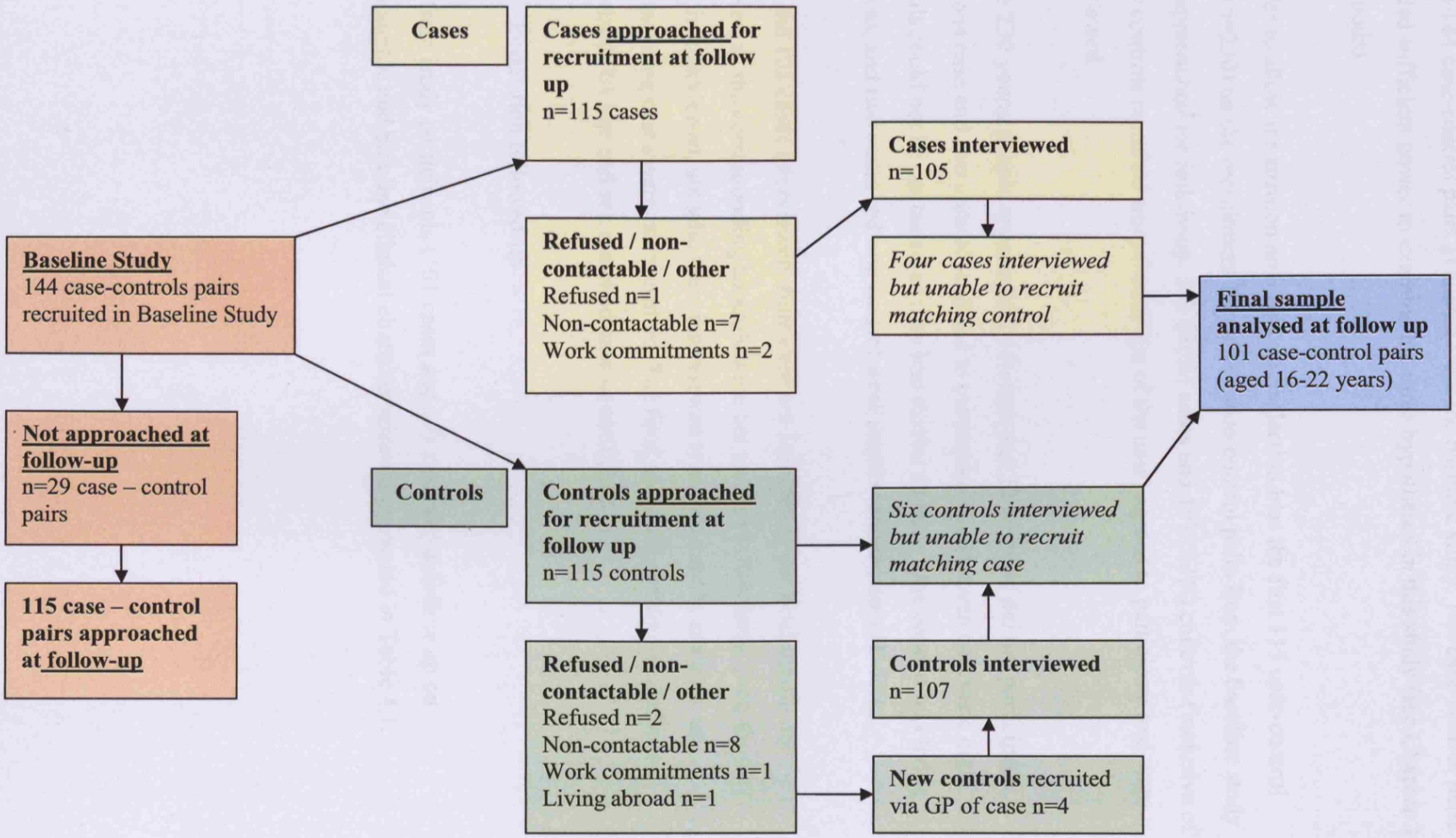
This chapter presents cross-sectional findings from the follow-up study including demographic information on both cases and controls and clinical information (cases only). The main body of this chapter encompasses description of the quantitative data collected from participants by questionnaires and cognitive tests in physical, psychological, social and neuropsychological domains.

Results of linear regression to investigate disease factors associated with poor outcome in cases are also presented in this chapter. Longitudinal analyses of measures given to participants at the baseline study and then again at follow-up (A-File and Social Support Questionnaire) are shown in Chapter 5.

4.2 Study population

4.2.1 Recruitment - See Figure 4.1 for recruitment breakdown.

Figure 4.1 **Flow chart showing number of cases and controls identified, contacted and recruited**



Of the 144 case-control pairs available from the baseline study, 100 case-control pairs provided sufficient power to examine the three hypotheses in this study (see Chapter 3 – Methods).

In order to allow for attrition and minimise selection bias the first 115 case-control pairs (n=230) on the recruitment list of 144 case-control pairs from the baseline study were approached for follow-up. 105 (91%) cases and 107 (93%) controls (inclusive of 4 new controls recruited from the GP list of the case) agreed to participate and were interviewed.

Of the 230 young people approached, 10 cases and 12 controls did not participate. Only one case and two controls refused to participate whilst seven cases and eight controls could not be contacted as they had moved address. One control was living overseas, and two cases and one control were unable to take time off work.

From the 105 cases interviewed, four were not included in the final sample for analyses, as the corresponding controls were not recruited. Similarly, from the 107 controls interviewed, six who were interviewed were not used in analyses, as corresponding cases were not recruited. The final sample therefore for analyses comprised 101 age and sex matched case-control pairs.

4.2.2 Population followed-up

Data from study participants (101 cases and 101 controls) at follow up on demographic and baseline clinical characteristics are presented in Table 4.1.

Table 4.1 Demographic and clinical details on cases and controls
All N are 101 for cases and controls except where specified

Category		Cases n (%)	Controls n (%)
Age (years)	16-18	40 (40)	39 (39)
	19-22	61 (60)	62 (61)
	Mean (SD)	19.3 (1.5)	19.4 (1.5)
Ethnicity			
White		91 (90)	93 (92)
Black Caribbean/African		4 (4)	3 (3)
Indian Asian		3 (3)	2 (2)
Others		3 (3)	3 (3)
Employment status			
Employed or self-employed		46 (45)	42 (41)
Unemployed or home duties		9 (9)	10 (10)
School student		16 (16)	15 (15)
University student		30 (30)	34 (34)
Socio-economic status (ownership of house and/or car)			
Not house or car		5 (5)	6 (6)
Own house, no car		4 (4)	4 (4)
Not house, >/=1 car		13 (13)	10 (10)
Own house, >/=1 car		78 (77)	78 (77)
Information not available at baseline		1(1)	3 (3)
Type of MD			
Meningitis Alone		33 (32)	
Meningitis & Septicaemia		40 (40)	
Septicaemia Alone		27 (27)	
Information was not available on clinical presentation		1 (1)	
SeroGroup			
SeroGroup B		47 (46)	
SeroGroup C		33 (33)	
SeroGroup Y		1 (1)	
Ungroupable		3 (3)	
Clinical diagnosis of MD only		17(17)	
Admitted to ICU [n=97]		52 (54)	
Median No of nights in intensive care (range)		2 (1-28)	

Cases and controls did not differ in age, ethnic minority status, employment status or socioeconomic status. Forty-seven pairs (46%) were male. Median time from baseline study interview to follow-up interview was 583 days (range 359-1225 days) for cases and 574 days (range 355-1211 days) for controls (not significantly different).

Case confirmation (seroGroup): Seventeen cases had only a clinical diagnosis of MD. Eighty-four cases had microbiologically confirmed MD seroGroup (see Chapter 3 – Methods for case definition).

Type of MD: Of the 101 cases, 40 had both meningitis and septicaemia, 33 had meningitis alone and 27 septicaemia alone. Information was not available on clinical presentation for 1 case.

Severity of disease (ICU admission): ICU admission and number of nights spent were used as measures of the severity of disease. Data were available on Intensive Care Unit (ICU) admission in 97 cases; 52 (54%) were admitted to ICU (median admission length 2 nights; range 1 to 28).

Venue for interview: 45 cases and 38 controls were interviewed at the test centre whereas 55 cases and 62 controls were interviewed at home.

4.2.3 Non-participating subjects from baseline study

Table 4.2 shows characteristics of non-participating subjects: (i) 10 cases and 12 controls from baseline study approached at follow-up but not recruited; and (ii) 29 cases and 29 controls not approached at follow-up for recruitment.

Table 4.2 Baseline demographic and clinical characteristics of non-participating subjects at follow up

	Approached not recruited		Not approached	
Category	**Cases lost (n=10) n (%)**	**Controls lost (n=12) n (%)**	**Cases lost (n=29) n (%)**	**Controls lost (n=29) n (%)**
Age (years) 15-17	6 (60)	7 (58)	14 (48)	15 (52)
18-19	4 (40)	5 (42)	15 (52)	14 (48)
Ethnicity				
White	7 (70)	10 (83)	28 (96.5)	27 (93)
Black Caribbean/African	1 (10)			
Indian Asian	1 (10)			1 (3)
Pakistani	1 (10)			
Others		2 (17)	1 (3.5)	1 (3)
Employment status				
Employed or self-employed	3 (30)	5 (42)	7 (24)	11 (38)
Unemployed or home duties	1 (10)	0	3 (10)	2 (7)
School student	4 (40)	4 (33)	9 (31)	10 (34)
University student	2 (20)	3 (25)	10 (35)	6 (21)
Socio-economic status (ownership of)				
Not house or car	3 (30)	3 (25)	3 (10)	1 (3)
Own house, no car		1 (8)	3 (10)	1 (3)
Not house, >/=1 car	1 (10)		7 (24)	5 (18)
Own house, >/=1 car	6 (60)	8 (67)	16 (56)	22 (76)
Type of MD				
Meningitis Alone	3 (30)		8 (28)	
Meningitis & Septicaemia	4 (40)		7 ((24)	
Septicaemia Alone	2 (20)		7 (24)	
Information was not available on clinical presentation	1 (10)		7 (24)	
SeroGroup				
SeroGroup B	5 (50)		13 (44)	
SeroGroup C	3 (30)		8 (28)	
SeroGroup Y				
SeroGroup W135	1 (10)			
Clinical diagnosis of MD only	1 (10)		8 (28)	
Admitted to ICU	4 (40)		6 (21)	
Median No of nights in intensive care (range)	4 (2-17)		3 (2-5)	

Efforts to recruit included first contact by telephone. If not contactable by phone, subjects were sent a short letter requesting confirmation of telephone number and participation. Potential participants were considered lost to follow-up in the case of failure to respond or where a reply was received reporting the young person had moved.

Those approached but not recruited were similar to recruited subjects in terms of age, sex, ethnicity and occupation disease types, serogroups, ICU admission or number of nights spent on ICU. Because of small numbers, these associations were not tested statistically. There was proportionally less home and car ownership (socioeconomic status) in cases approached but not recruited (10%) compared to cases recruited (30%).

4.2.4 Baseline subjects not approached at follow-up

Details of baseline subjects not approached at follow up are shown in Table 4.2. Those not approached were similar to recruited subjects in terms of age, sex, ethnicity, socio-economic status and occupation, disease types and serogroups. Because of small numbers, these associations were not tested statistically. However, proportionally, cases recruited were more likely to have been admitted to ICU (54%) than cases not approached (21%).

4.3 Outcomes from cross-sectional analyses

The following describes the outcomes from quantitative data collected from participants by questionnaires and tests in social, psychological, neuropsychological and physical domains. Whether a subject was interviewed in the study centre (cases n=45 [45%], controls n=38 [38%]) or at home (cases n=55 [55%], controls n=62 [62%]) was not associated with any measured outcomes.

4.3.1 Social behaviour and health risk behaviours

Data regarding social and sport activities, days off work, school or college, living arrangements and health behaviours in cases and controls at follow up are shown in Table 4.3. Analyses were conducted using Fisher's exact test.

There were no significant group differences between cases and controls on any measures of social activity or leisure. There were also no significant differences in reported health risk behaviours including smoking, drinking alcohol or drug use in the 2 weeks before interview. However, there was a trend ($p=0.08$) for more controls (70%) than cases (57%) to have attended a party or nightclub in the 2 weeks prior to interview.

Table 4.3 Social and health behaviours in cases and controls at follow-up

Measure	Variables	Cases N=101 n (%)	Controls N=101 n (%)	P value
Social Activities				
	Attendance at Social activities *In 2 weeks preceding interview*			
	Pub / bar	90 (89)	86 (85)	0.5
	Disco / Nightclub / Party	58 (57)	71 (70)	0.08
	Youth Club	0	4 (4)	0.12
	Group Activities	70 (69)	74 (73)	0.5
	Religious ceremonies	8 (8)	15 (15)	0.18
Sporting activities				
	Participated in sport activities *In 2 weeks preceding interview*	41 (41)	39 (39)	0.9
Living arrangements				
	Living with family	83 (82)	76 (75)	0.5
	Living Independently			
	By self or with partner	6 (6)	8 (8)	0.5
	With friend	12 (12)	17 (17)	0.5
School or work absences				
	Missed days from work/ school / college *In 3 months preceding interview*			
	Total sample responding yes (%)	31 (31)	30 (30)	1
Health Behaviours				
	Consider self to be a smoker	45 (45)	41 (41)	0.7
	Regular use of recreational drugs	14 (14)	19 (19)	0.5
	Drank alcohol *In 2 weeks preceding interview*	84 (83)	86 (85)	0.9

4.3.1.1 Social support

Mean and SD scores for cases and controls on social support variables are presented in Table 4.4. Analyses were conducted using Independent *t*-tests. Statistically significant p-values are in boldface.

Subscale scores of the Social Support Questionnaire 6 (SSQ6) (Sarason *et al.* 1987) assess the number of 'available others' the subject feels he or she can turn to in times of need in different situations. The questionnaire also assesses perceived satisfaction with available support.

A total Satisfaction subscale score was obtained by calculating the mean across all six satisfaction ratings (a maximum mean score of 6). The total Network score was obtained by summing the number of people reported in each of the six subscales and dividing by six, which is the number of subscales on the SSQ6. The Total Support Score was obtained by combining the number of people reported for each subscale and satisfaction rating and dividing by 12 to provide a mean score (see Chapter 3 – Methods).

Table 4.4 **Mean ± SD Subject scores on SSQ6**
Higher score indicates greater support

Measure	Subscales	Possible Range	Cases N=101 Mean (SD)	Controls N=101 Mean (SD)	P value
Mean (SD)	**Satisfaction score**	0-6	5.2 (0.9)	5.5 (0.7)	0.06
	Females		5.4 (0.8)	5.6 (0.8)	0.3
	Males		5.0 (1.0)	5.3 (0.6)	0.12
	Average number of supports	0-9	3.2 (1.4)	3.6 (1.3)	**0.03**
	Females		3.3 (1.3)	3.6 (1.2)	0.18
	Males		3.1 (1.5)	3.6 (1.4)	0.08
	Total score	0-7.5	4.0 (1.1)	4.4 (0.9)	**0.01**
	Females		4.1 (1.0)	4.4 (0.82)	0.13
	Males		3.9 (1.2)	4.3 (1)	0.05

Cases had significantly fewer people in their social network and lower total support scores. There was a trend for cases to be less satisfied with the degree of social support available. As gender differences are reported in the literature in levels of social support (Colarossi and Eccles 2000;Geckova *et al.* 2003; Piko 1998), group

differences by sex was examined. A trend was found for male cases to report a lower network (p=0.08) and total score (p=0.05) compared to male controls.

4.3.2 Psychological outcomes

Data were available on 3 psychological outcome measures, Beck Depression Inventory (BDI-II) (Beck *et al.* 1996); the Mental Health Dimensions and Mental Component Summary score of the SF36 (Jenkinson *et al.* 1996); and the Clinical Outcome Research Evaluation (CORE) questionnaire (Core System Group 1998).

4.3.2.1 Beck Depression Inventory –II (BDI-II)

The mean (SD) BDI-II scores are presented in Table 4.5. Higher score indicates higher levels of depressive symptomatology. A cut-off score of greater than 13 is recommended as indicative of caseness (see Chapter 3 – Methods). Scores can be categorised as falling within mild depression (14-19), moderate depression (20-28), or severe depression (29-63). Analyses were conducted using Independent *t*-tests and Fisher's exact tests for proportions. Statistically significant p-values are in boldface.

Table 4.5 Subject scores on Beck Depression Inventory

Measure	Variables	Test score range	Cases N=101	Controls N=101	P value
All subjects	Mean (SD)	0-63	8.04 (7)	6.9 (6)	0.2
	Number (%) rating >13		20 (20)	12 (12)	0.18
	Number of females rating >13 N (%)		14 (26)	8 (15)	0.16
	Number of males rating >13 N (%)		6 (13)	4 (9)	0.5

Mean BDI scores did not differ significantly between cases and controls. However, nearly twice as many cases as controls (20% vs. 12%) reported depressive symptoms that were in the clinical range, although this failed to reach significance. As marked gender differences in the prevalence of depressive symptoms are well known (Baron and Perron 1986;Rutter 1985; Rutter 1986;Teri 1982) group differences by gender was examined. No significant differences were found.

4.3.2.2 *Associations between MD and depressive symptoms adjusted for other risk factors*

The association of MD with depression was further examined after adjustment for other factors known to be strong risk factors for depression.

Table 4.6 shows a series of logistic regression analyses of depressive symptoms (BDI score >13) regressed onto variables known to be risk factors for depression, including life stress (Brown and Harris 1978), female gender and age (Baron and Perron 1986; Lewinsohn *et al.* 1998), and socioeconomic status (SES). These are initially unadjusted for age at follow-up, then partially adjusted, then in an "all-in" multivariate model. Data shown are Odds Ratios (OR) and 95% (CI). Statistically significant p-values are in bold.

Table 4.6 Associations between MD, stress and depressive symptoms

	Univariate associations		**OR adjusted for age and gender**		**Multi-variable model: OR adjusted for all other factors**	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Meningococcal disease	1.9 (0.9, 4.1)	0.1	1.9 (0.9, 4.2)	0.10	2.6 (1.1, 6.2)	**0.03**
Female sex	2.0 (0.9, 4.4)	0.08	2.0 (0.9, 4.4)	0.10	2.8 (1.1, 7.2)	**0.04**
High socioeconomic status (SES)	2.3 (0.3, 18.8)	0.4	2.3 (0.3, 18.9)	0.4	4.1 (0.6, 4.2)	0.2
Age at follow-up	0.89 (0.70, 1.16)	0.4	0.95 (0.74, 1.23)	0.7	0.97 (0.73, 1.32)	0.9
Stress						
Stress total score follow-up	1.16 (1.07, 1.27)	**<0.001**	**1.19 (1.09, 1.30)**	**<0.001**	**1.25 (1.13, 1.38)**	**<0.001**

The table shows that MD increases the risk of depression in cases when adjusted for gender, age, SES and stress. MD and stress each independently increase risk of depression and therefore, stress has confounded the association of MD with depression.

The SF-36 mental health dimensions and Mental Component Summary score (MCS):

Data on the mental health dimensions of the SF36 and the Mental Health Component Summary score are presented in Table 4.7. Analyses were conducted using Independent *t*-tests. Statistically significant p-values are in boldface.

The SF36 rates mental and physical well-being along eight dimensions of health. The eight dimension scores can be further aggregated into a component summary score: the physical component summary score and the mental health component summary score (Ware *et al.* 1994) derived by principal components analysis. The aggregated summary scores are then transformed to a mean of 50 and a standard deviation of 10. This process is aimed at producing the two summary scales while losing a minimum of information (see Chapter 3 – Methods).

Table 4.7 Mean ± SD subject scores on the SF36 Mental Health Dimensions and Mental Component Summary (MCS)

Higher score indicates better health status

Measure	Variables	Test score range	Cases N=101 Mean (SD)	Controls N=101 Mean (SD)	P value
SF36	**Dimension Score**	0-100			
	Social functioning		88.2 (15)	90.0 (14)	0.3
	Mental health functioning		71.0 (16)	74.3 (15)	0.1
	Role limitation due to emotional problems		83.5 (33)	79.5 (33)	0.3
	Energy and vitality		58.9 (19)	60.7 (16)	0.4
	Mental Component Summary				
	Total Sample		46.6 (30)	53.5 (24)	0.07
	Females		41.2 (33)	51.7 (24)	0.05
	Males		52.9 (20)	55.7 (24)	0.5

There were no significant differences in the scores on the four mental health dimensions of the SF36 which includes mental health (feelings of nervousness and depression); role limitation with work or other daily activities due to emotional problems, social function (interference with normal social activities due to physical or emotional problems) and vitality (feeling tired and worn down). However, on the MCS score which is the aggregate summary of scores for the four dimensions there

was trend for cases to have a lower score than controls denoting more problems in these areas and poorer mental health. As gender differences in mental health are well described (Baron and Perron 1986;Rutter 1985; Rutter 1986;Teri 1982), group differences by sex were examined, revealing female cases to have a lower MCS score than female controls (p=0.05).

Clinical Outcome Research Evaluation Outcome Measure (CORE-OM):

Data from the CORE-OM are presented in Table 4.8. Analyses were conducted using Independent *t*-tests. Wilcoxon-Mann-Whitney tests were performed on data not normally distributed.

The CORE-OM is a 34-item self-report measure assessing general psychological functioning in four domains: subjective well-being, problems or symptoms, functioning, and risk to self and others. It has been widely used to measure emotional disturbance in service settings delivering psychological interventions in primary and secondary care (Barkham *et al.* 1998;Barkham *et al.* 2001;Evans *et al.* 2002) (see Chapter 3 – Methods).

Table 4.8 **Mean ± SD subject scores on CORE-OM**
Higher score indicates more problems and distress

Variable	Test score range	Cases N=101 Mean (SD)	Controls N=101 Mean (SD)	P value
Domains				
Subjective well-being	0-4	1.0 (0.7)	0.9 (0.6)	0.17
Problems or Symptoms	0-4	0.8 (0.6)	0.7 (0.6)	0.2
Life Functioning	0-4	0.8 (0.5)	0.7 (0.5)	0.4
Risk / harm *(suicidal ideation and harm to self and others)*	0-4	0.1 (0.2)	0.1 (0.3)	1
Total Score	0-4			
Total Sample		0.7 (0.4)	0.6 (0.4)	0.2
Females		0.8 (0.5)	0.7 (0.4)	0.16
Males		0.6 (0.4)	0.6 (0.4)	1

No significant group differences were noted on the four dimensions of the CORE-OM psychological scale. As sex differences in domain scores have been reported on the CORE-OM (Evans *et al.* 2002), group differences by sex were examined and no significant differences found.

Personal and Family Life Stress:

Data for the Adolescent Family Inventory of Life Events (A-FILE) (McCubbin *et al.* 1982) are presented in Table 4.9. Data shown are mean ± SD scores on the A-FILE with total scores on stress and distress for events in the family in the year preceding interview. Analyses were conducted using Independent *t*-tests. Wilcoxon-Mann-Whitney tests were performed on data not normally distributed.

The A-FILE assesses the number of stressful events and the distress they elicit in six domains of family life (see Methods section). A total stress score reflects an accrual of life events and changes occurring in the family: transitions of family members, sexuality, losses, responsibilities and strains, substance use and legal conflict.

Table 4.9 **Mean ± SD subject scores on A-FILE**
Higher scores indicate more stressful events and distress

Measure	Subscales	Score Range	Cases N=101	Controls N=101	P value
Stress					
	Family transitions	0-4	1.5 (1.4)	1.8 (1.5)	0.15
	Family sexual matters	0-4	0.2 (0.5)	0.2 (0.5)	1
	Family losses	0-7	0.6 (0.1)	0.7 (0.1)	0.3
	Family responsibilities	0-19	3.1 (3)	3.8(3)	0.08
	Stresses at school and substance abuse	0-4	0.5 (0.8)	0.5 (0.8)	0.8
	Family legal stresses	0-2	0.1 (0.4)	0.2 (0.4)	0.2
Total stress score	Total sample	0-50	6.0 (4)	7.1 (5)	0.05
	Females		5.7 (4)	6.8 (4)	0.11
	Males		6.3 (4)	7.4 (5)	0.2
Total distress score*	Total Sample	0-500	24.0 (23)	30.4 (29)	0.08
	Females		26.8 (22)	30.4 (26)	0.4
	Males		20.8(23)	30.5 (32)	0.10

*Each event [50 in total] rated on a scale of 0-10 - *high score indicates greater distress*

Cases had lower levels of life stress than controls, although this narrowly missed significance (P=0.05).

To investigate this finding further exploratory analysis was undertaken. The possibility that cases were exposed to fewer controllable life events was explored (see Table 4.10). Data shown are mean ± SD scores on the A-FILE for the number of stressful events (controllable and uncontrollable) in the family in the year preceding interview. Analyses were conducted using Independent *t*-tests.

The events of the A-FILE were therefore divided into controllable life events (i.e. starting a new school, parent going to college or starting new job) and uncontrollable life events outside the family (i.e. deaths, legal trouble, family illness). The results demonstrate that cases reported fewer controllable events in the year preceding interview than controls, which approached significance (p=0.05) with a trend towards experiencing fewer uncontrollable events (p=0.07). The Total Stress score (for both controllable and uncontrollable events combined) was lower in cases compared to controls (p=0.05). It is not possible to determine the possible underlying reasons.

Table 4.10 Mean ± SD subject scores on Stressful Events within the Family on the A-FILE

Measure	Variables	Number of Events	Cases N=101	Controls N=101	P value
A-FILE Stressful Events	**Controllable events**	**30**			
	Family transitions	11	1.2 (1.2)	1.4 (1.2)	0.2
	Family sexual matters	2	0.14 (0.35)	0.14 (0.37)	1
	Family losses	1	0.02 (0.14)	0.05 (0.22)	0.2
	Family responsibilities	12	1.7 (2)	2.2 (2.2)	0.08
	Stresses at school and substance abuse	4	0.44 (0.75)	0.51 (0.87)	0.5
	Total	**30**	**3.5 (2.6)**	**4.2(3.1)**	**0.05**
	Uncontrollable events	**20**			
	Family transitions	3	0.32 (0.51)	0.40 (0.60)	0.3
	Family sexual matters	2	0.1 (0.29)	0.1 (0.29)	1
	Family losses	6	0.53 (0.74)	0.61 (0.77)	0.4
	Family responsibilities	7	1.2 (1.3)	1.5 (1.4)	0.2
	Family legal stresses	2	0.1 (0.36)	0.17 (0.43)	0.2
	Total	**20**	**2.5 (1.7)**	**2.9 (2.2)**	**0.07**
	Total Stress score	**50**	**6.0 (4)**	**7.1 (5)**	**0.05**

4.3.3 Quality of life

Quality of life data are presented in Table 4.11. Data shown are median scores or mean ± SD where appropriate for quality of life (QOL) compared with baseline and compared with peers. Analyses were conducted using Independent *t*-tests. Wilcoxon-Mann-Whitney tests were performed on data not normally distributed. Statistically significant p-values are in boldface.

Subjects were asked to rate their current global QOL on a Likert scale compared to their peers and whether their QOL had changed since the time of the baseline study (see Chapter 3 – Methods).

Table 4.11 Subject scores on Quality of Life (QOL)
Higher score indicates better QOL

Measure	Subscales	Test Score Range	Cases N=101	Controls N=101	P value
Median (range)	**QOL compared with baseline** (for cases, before MD)	-5 to +5	-0.1 (-5 to 3)	0.96 (-3 to 3)	**<0.0001**
	Females		-1 (-4, 3)	0.8 (-3, 3)	**0.001**
	Males		-0.90 (-5,3)	0.97 (-3, 2)	**0.01**
Mean (SD)	**QOL compared with your peers** (for cases, those without MD)	-5 to +5	-0.80 (1.37)	-0.31 (1.26)	**<0.001**
	Females		-0.90(1.43)	-0.42 (1.30)	0.07
	Males		-0.68 (1.29)	-0.19 (1.22)	0.06

Cases reported that overall quality of life was significantly worse than peers and unlike controls, had not improved since the baseline study. This was true for both male and female cases.

When stratified for gender, both male and female cases felt their quality of life was significantly poorer than baseline compared to controls. There was a trend for male (p=0.06) and female (p=0.07) cases to report lower QOL compared to peers.

As QOL is complex and composed of multiple dimensions, MD survivors were asked additional descriptive questions: w*hether home life, friendships, academic achievements, leisure activities, vocational achievements, and physical ability had been affected since having MD.* Forty-nine percent of cases said home life has been affected since MD; 41% friendships; 53% leisure activities; 41% vocational achievements; 54% physical ability; and 49% academic achievements (see Table 4.12). Data shown are numbers and percentages for areas of life affected or unaffected since MD.

Table 4.12 Subject scores on self-reported areas of life affected since MD

Domains	Not at all N (%)	Only a little N (%)	Quite a lot N (%)	A Great deal N (%)
Home life	52 (51)	36 (36)	7 (7)	6 (6)
Friendships	60 (59)	24 (24)	12 (12)	5 (5)
Academic achievements	52 (51)	30 (30)	14 (14)	5 (5)
Leisure activities	48 (47)	35 (35)	14 (14)	4 (4)
Vocational achievements	60 (59)	28 (28)	6 (6)	7 (7)
Physical ability	47 (46)	36 (36)	10 (10)	8 (8)

4.3.4 Educational outcomes

Data for educational outcomes are shown in Table 4.13. Data shown are mean ± SD and percentages. Analyses were conducted using Independent *t*-test, and Fisher's exact test for proportions. Wilcoxon-Mann-Whitney tests were performed on data not normally distributed. Statistically significant p-values are in boldface.

Table 4.13 Educational outcomes of cases and controls

Measure	Subscales		Cases N=101	Controls N=101	P value
Educational Outcomes					
	Number of passes achieved at GCSE level (range 0-13)	mean (SD)	8 (3)	9 (3)	**0.02**
	Percent of subjects post secondary education without A-Levels		64	50	0.07
	Percent who failed exams in the previous year		19	8	**0.04**
Self rating of education subsequent to MD	Average N (%) Below average N (%) Above average N (%)		70 (69) 5 (5) 26 (26)	59 (58) 4 (4) 38 (38)	0.18

Cases achieved significantly fewer passes at GCSE level and were more likely to have failed an exam in the previous 12 months. Of those who had completed their

secondary education after the baseline study, 64% of cases compared to 50% controls did not attain any A levels.

Cases and controls were asked to rate their academic achievement post-MD. No differences were found between cases and controls in this regard.

4.3.5 Physical outcomes

Data were available on physical health outcomes from three sources: the Annotated Scale of Bodily Injuries Regulation (ASBIR) (Erickson and De Wals 1998); the Physical Component Summary (PCS) score from the SF36 (Jenkinson *et al.* 1996); and the Chalder Fatigue Scale (Chalder *et al.* 1993).

4.3.5.1 Annotated Scale of Physical Injuries Regulation

ASBIR data are shown in Table 4.14. The data shown are percentages of cases who reported physical injuries. The percentage increases with severity of permanent injury. Cases may report >1 deficit.

The ASBIR is an evaluation system developed by the Quebec Occupational Health and Safety Commission for assessing work-related injuries and used in outcome studies of MD to assess physical injury (Erickson and De Wals 1998; Erickson *et al.* 2001). The ASBIR provided a quantitative estimate of physical injury and disability (in cases), including anatomic and physiologic deficits, disfigurement and suffering or loss of enjoyment of life.

Table 4.14 Subject scores on the ASBIR

Annotated Scale of Bodily Injury (ASBIR)		Cases N (%)
	Cases reporting physical sequelae	*N = 58*
	Symptoms consistent with Raynaud's disease *(colour or temperature change or pain in hands or feet in response to cold)*	28 (48.3)
	Skin scarring	18 (31)
	Vertigo symptoms	17 (29.3)
	Mobility problems	13 (22.4)
	Speech problems	13 (22.4)
	Hearing problems	12 (20.7)
	Amputations	3 (5.2)
	Epileptic episodes	2 (3.5)
	Impairment in upper limb function	4 (7)

Fifty-seven percent of survivors (n=58) had physical sequelae as reported on the ASBIR. Cases reported a range of injuries from minor scarring to bilateral amputations. A number of cases reported multiple physical symptoms (see Table 4.15).

Table 4.15 Number of reported sequelae in cases (n=58)

Cases N (%)	Number of reported symptoms	Total number of reported symptoms
3 (5)	5	15
3 (5)	4	12
4 (7)	3	12
23 (40)	2	46
25 (43)	1	25
58 (100)		**110**

The most frequently reported physical injuries were symptoms consistent with Raynaud's disease, followed by skin scarring (on their face, scalp/skull, neck, arms, shoulder and elbows, forearms and wrists, hands, trunk and lower limbs). In addition, cases reported mobility problems, speech problems, impairment in upper limb

function, hearing problems and symptoms of vertigo. The least reported sequelae being epileptic episodes and amputation (bi-lateral amputations of the lower leg).

4.3.5.2 SF36 Physical Domain scores and Physical Component Summary (PCS) score

Data on the physical domains of the SF36 and the Physical Component Summary score are presented in Table 4.16. Data shown are mean ± SD. Analyses were conducted using Independent *t*-tests. Statistically significant p-values are in boldface. A Higher score for each domain indicates better health status from 0 (worst possible health state) to 100 (best possible health state).

The SF36 rates mental and physical well-being along eight dimensions of health. The eight dimension scores can be further aggregated into a component summary score: the physical component summary score and the mental health component summary score (Ware *et al.* 1994) derived by principal components analysis. The aggregated summary scores are then transformed to a mean of 50 and a standard deviation of 10. This process is aimed at producing the two summary scales while losing a minimum of information (see Chapter 3 – Methods).

Table 4.16 Mean ± SD subject scores on the SF-36 Physical Domain and Physical Component Summary

Measure	Subscales	Score Range	Cases N=101	Controls N=101	P value
SF36		0-100			
PCS Domain scores	General health perception		62.2 (20.4)	70.3 (18.8)	**<0.01**
	Physical functioning		91 (13.7)	92 (14.7)	0.6
	Bodily pain		78.8 (21.6)	81.5 (17.2)	0.3
	Role limitations due to physical functioning		85.6 (27.7)	87.9 (27.3)	0.5
Physical Component Summary (PCS)	Total		48.4 (29.8)	51.8 (26)	0.4
PCS by gender	Females		42.6 (34)	49.7 (27.2)	0.2
	Males		55.2 (22.5)	54.2 (24.6)	0.8

No significant group differences were noted in the physical domain scores except general health perception which was significantly poorer in cases compared to controls (p=<0.01). The summary score (PCS) for the four dimensions was not significantly different between cases and controls and no differences were found when stratified by gender.

4.3.5.2.1 Change in health status in previous year

A single item of the SF36 related to change in subjects' health over the past year. This item is scored separately and is not included in the PCS or MCS scores. Forty-four percent of cases compared to 23% of controls reported that overall their health status had improved in the year preceding interview (p = <0.001, Fisher's exact test).

4.3.5.3 Fatigue

Mean ± SD scores on daily fatigue and energy levels in cases and controls are presented in Table 4.17. Analyses were conducted using Independent *t*-tests. Wilcoxon Mann-Whitney tests were performed on data not normally distributed. Statistically significant p-values are in boldface.

The Chalder Fatigue Scale (Chalder *et al.* 1993) is a self-report instrument in which subjects are asked to rate the extent to which fatigue has caused problems for them in relation to exemplar statements as a measure of physical and mental fatigue. The Fatigue Scale produces a total score, a score reflecting mental and physical fatigue as well as separate sub-scale scores for mental fatigue and physical fatigue. The questionnaire comprises 11 items, each of them being quantified on a scale of 0 to 3 (scored in a Likert format with response options ranging from better than usual to much worse than usual). Thus, the maximum score is 33 (see Chapter 3 Methods).

Table 4.17 Mean ± SD subject scores on the Fatigue Scale
Higher scores denote greater fatigue

Measure	Subscales	Test Score Range	Cases N=101 Mean (SD)	Controls N=101 Mean (SD)	P value*
Physical fatigue score	Problems with tiredness	0 – 3	1.5 (0.6)	1.4 (0.6)	0.09
	Need to rest		1.4 (0.5)	1.3 (0.6)	0.3
	Problems starting things		1.2 (0.6)	1.1 (0.6)	0.3
	Lacking in energy		1.3 (0.6)	1.2 (0.6)	0.4
	Less strength in muscles		1.1 (0.6)	1.0 (0.5)	0.4
	Feeling sleepy		1.5 (0.6)	1.4 (0.6)	0.2
	Feeling weak		1.1 (0.5)	1.0 (0.6)	0.14
	Total Physical Fatigue score	0 – 21	9.1 (3)	8.4 (3)	0.13
Mental fatigue score	Problems in thinking clearly	0 – 3	1.2 (0.6)	1.0 (0.4)	0.08
	Poorer memory		1.0 (0.5)	0.9 (0.4)	**0.01**
	Making more slips of the tongue		1.2 (0.6)	1.0 (0.5)	**0.02**
	Difficulty concentrating		1.2 (0.6)	1.1 (0.5)	0.12
	Total Mental Fatigue score	0 – 12	4.6 (1.9)	4 (1.2)	**0.01**
Total fatigue score (physical and mental fatigue)	**Total**	0 – 33	13.7 (5)	12.3 (4)	**0.04**
	Females		14.1 (5)	12.7 (4)	0.10
	Males		13.0 (4)	12.0 (4)	0.2

Cases had a significantly higher total fatigue score compared to controls. When subscales were examined, cases had greater mental fatigue, were more prone to making slips of the tongue, and experienced poorer memory. A trend for cases to have problems in thinking clearly (p=0.08) was also noted. Further, there was a trend for cases to have more problems with physical tiredness (p=0.09).

A number of reports have shown that complaints of fatigue are greater in adolescent females than males (Kobayashi and Demura 2006; Monden 1990;Takakura 1997). Accordingly, gender differences were examined. No gender differences in total fatigue scores were found between cases and controls.

4.3.6 Neuropsychological outcomes

This section describes the quantitative data collected on cognitive tests for cases and controls. A comprehensive battery of neuropsychological tests was administered to assess intellectual ability (premorbid and current), executive function, psychomotor speed, visuospatial functioning, attention and memory in both the verbal and visual domains.

Table 4.18 summarises the neuropsychological tests administered at follow-up to cases and controls (see Chapter 3 – Methods).

Table 4.18 Neuropsychological tests administered to cases and controls

*Cambridge Neuropsychological Test Automated Battery (CANTAB) (Fray *et al.* 1997)

4.3.6.1 Laterality

Laterality (in which certain functions such as language comprehension are localised on one side of the brain in preference to the other) has been shown to affect cognitive abilities (McManus *et al.* 1983;McManus *et al.* 1993). Laterality was assessed in cases and controls on the basis of hand preferences quantified using a questionnaire (Crovitz and Zener 1962). Scores range from 18-90 (see Chapter 3 – Methods).

No significant differences were found in handedness between cases and controls with 80% of cases and controls being predominantly right-handed, 10 % indicating a mixed hand preference and 10% indicating a strong left hand preference. The expected proportion with a right hand preference (score <30) in the normal population is 90%. The median score for cases was 27 (range 18-89) and for controls 28 (range 18-82).

4.3.6.2 Intellectual ability

Premorbid intellectual ability was assessed using the National Adult Reading Test (NART) (Nelson and Willison 1991). The NART is a test of verbal ability and provides an accurate measure of premorbid IQ by assessing the ability to read 50 non-phonetic words (irregularly spelt words). An estimate of premorbid IQ is derived from the number of errors. Reading ability has been shown to be relatively well preserved in brain injury (Nelson *et al.* 1978).

Current intelligence ability was estimated using 2 subtests (Vocabulary and Block Design) from the Wechsler Adult Intelligence Scale – Revised (WAIS-R) Short Form (Brooker *et al.* 1986; Sattler 1988; Silverstein *et al.* 1982; Wechsler 1981). Vocabulary is a test of verbal knowledge and Block Design a measure of perceptual organisation. The two subtests are frequently used for estimating IQ because the tests' measure of IQ correlates (.90) with Full-Scale IQ based on all of the subtests of the WAIS (Hoffman *et al.* 1988;Missar *et al.* 1994;Sattler 1988).

Raw scores from both the NART and the WAIS were converted into a scaled score with an average of 100 (SD 15), (see Chapter 3 – Methods).

Data on the premorbid and current estimates of intellectual ability are shown in Table 4.19. Data shown are mean ± SD. Analyses were conducted using Independent *t*-tests.

Table 4.19 Subject scores on intellectual ability

Variable	Measure	Cases N=101 Mean (SD)	Controls N=101 Mean (SD)	P value
Pre-morbid estimate	National Adult Reading Test (NART)	96.7 (10.9)	99.2 (10.9)	0.11
Current estimate	Wechsler Adult Intelligence Scale - Revised Short Form (WAIS-R)	102.1 (11.6)	104.3 (10.2)	0.15

Data were normally distributed with no difference found between cases and controls.

4.3.6.3 Memory

Short and long-term verbal memory were assessed using the Rey Auditory Verbal Learning Test (RAVLT) (Rey 1941;Rey 1964;Taylor 1959). Short-term visual memory was assessed using four tests from Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian and Owen 1992). Tests included Delayed Matching to Sample assessing both simultaneous and short-term visual memory, Spatial Recognition Memory assessing recognition memory for spatial locations and Pattern Recognition Memory assessing recognition memory for patterns. Long-term visual memory was assessed using the recall and recognition subtests from the Rey-Osterrieth Complex Figure (ROCF) test (Osterrieth 1944;Rey 1941;Taylor 1959) and the Paired Associate Learning from CANTAB assessing episodic memory, (see Chapter 3 – Methods).

Data on short and long-term visual and verbal memory are presented in Table 4.20. Data shown are means ± SD unless otherwise stated. Analyses were conducted using Independent *t*-tests, and Fisher's exact test for proportions. Statistically significant p-values are in boldface.

Table 4.20 Subject scores on cognitive tests of memory

Variable	Measure	Score Range	Cases N=101 Mean (SD)	Controls N=101 Mean (SD)	P value	Direction of Difference - cases compared to controls
VERBAL MEMORY						
	Short-term					
	RAVLT					
	Immediate Memory Recall (Trial 1)	0-15	7.4 (1.9)	7.5 (2)	0.7	
	Interference Trial (Trial 6 / List B)		5.9 (1.8)	6.5 (1.7)	**0.04**	Worse
	Long-term					
	Delay trial (30 minutes)		11.5 (2.5)	11.5 (2.4)	1	
VISUAL MEMORY						
	Short-term					
	CANTAB					
	Delayed Matching to Sample					
	Mean latency time – all delays (milliseconds)		3378 (971)	3194 (878)	0.16	
	Percentage of correct responses (all delays)		81.7	82.7	0.4	
	Spatial Recognition Memory					
	Percentage of correct responses		84	85	0.5	
	Pattern Recognition Memory					
	Percentage of correct responses		90.7	92.5	0.13	
	Long-term visuospatial associative memory					
	Paired Associates Learning					
	All stages completed %		100	98	0.5	
	Total errors (adjusted)		6.5 (5.6)	6.3 (8)	0.19	
	ROCF					
	Recall (40 minutes delay)	0-36	16.6 (5.3)	18.6 (4.8)	**<0.01**	Worse
	Recognition	0-24	20.8 (1.9)	21 (1.8)	0.3	

Verbal memory:

Short-term: Cases recalled significantly fewer words on the Interference Trial of the RAVLT compared to controls. No differences were found between cases and controls on the Immediate Memory Recall Trial of the RAVLT.

Long-term: No differences were noted between cases and controls on the Delay Trial of the RAVLT.

Visual memory:

Short-term: No differences were found between cases and controls on tests assessing short-term visual memory (Delayed Matching to Sample, Spatial and Pattern Recognition Memory) with both groups comparable in the number correct responses achieved and latency times.

Long-term: Cases achieved significantly lower scores on the recall subtest of the Rey-Osterrieth Complex Figure test compared to controls. No differences were found on the recognition part of the test where participants are presented with correct and incorrect details of the drawing and asked to recognise if they featured in the original drawing. Similarly, no differences were found between cases and controls on the Paired Associates Learning test with both groups completing all stages of the test with similar overall error rates.

4.3.6.4 Attention

Attention was assessed using two tests from the CANTAB (Sahakian and Owen 1992): Rapid Visual Information Processing assessing sustained attention; and Matching to Sample assessing selective attention.

Sustained attention: Three measures are reported for the Rapid Visual Information Processing (RVP) test. Two sensitivity measures: RVP 'A' which assesses the ability to detect target sequences and the RVP 'B' assessing the subject's tendency to respond regardless of whether target sequence is present. Both measures are based on the proportion of hits and the proportion of false alarms of the responses made during the RVP test. The mean time taken to respond was also measured.

Selective attention: Matching to Sample is a simultaneous visual search task. Two measures are reported: the percentage of correct responses and the response latency. Efficient performance on this task requires the ability to search among the targets and ignore the distractor patterns, which have elements in common with the target. As this task includes both speed and accuracy demands, subjects may trade-off speed of response in favour of accuracy, or vice versa (see Methods Section).

Data on tests of sustained and selective attention are presented in Table 4.21. Data shown in this table are mean ± SD unless otherwise stated. Analyses were conducted using Independent *t*-tests, and Fisher's exact test for proportions. Wilcoxon-Mann-Whitney test was performed on data not normally distributed.

Table 4.21 Subject scores on CANTAB tests of attention

Variable	Measure	Score Range	Cases N=101 Mean (SD)	Controls N=101 Mean (SD)	P value	Direction of Difference - cases compared to controls
Sustained Attention	Rapid Visual Information Processing (RVP)					
	RVP 'A' Detecting target sequences	0 to 1	0.89 (0.05)	0.90 (0.05)	**0.01**	Slower
	RVP 'B' Tendency to respond regardless of whether target sequence is present	-1.00 to +1.00	0.93 (0.1)	0.89 (0.2)	0.3	
	Mean latency to respond (time in milliseconds)		439 (92)	436 (104)	0.5	
Selective attention	Matching to Sample					
	Mean latency time (milliseconds)		1600 (479)	1460 (372)	**0.02**	Slower
	Percentage of correct responses		93.7	93.6	0.8	

Sustained attention: Cases detected significantly fewer targets than controls on the sensitivity index measure A' on the Rapid Visual Processing task. No differences were found between cases and controls on the sensitivity index measure B' or on the response time on this test.

Selective attention: Cases were significantly slower than controls in touching the screen for correct trials on Matching to Sample task measuring selective attention, although no difference in accuracy was found as both groups achieved the same number of correct responses.

4.3.6.5 Executive function

Four tests from the CANTAB (Sahakian and Owen 1992) were administered to evaluate executive function: Intra-Extra Dimensional Set Shift is primarily a test of attentional flexibility, assessing rule acquisition and attentional set shifting; Spatial Working Memory assesses working memory and strategy use; Stockings of Cambridge assesses spatial problem-solving ability and motor control; and the Spatial Span test assesses working memory capacity (see Chapter 3 – Methods).

Data on executive function tests are shown in Table 4.22. Data shown in this table are mean ± SD on cognitive tests of executive functioning. Analyses were conducted using Independent *t*-tests. Wilcoxon-Mann-Whitney test was performed on data not normally distributed. Statistically significant p-values are in boldface.

Table 4.22 Subject scores on CANTAB tests of executive function

Variable	Measure	Score Range	Cases N=101 Mean (SD)	Controls N=101 Mean (SD)	P value	Direction of Difference - cases compared to controls
Rule acquisition and attentional set shifting ability	Intra/ Extra Dimensional Shift					
	Stages completed	0-9	8.4 (1.2)	8.4 (1.3)	0.9	
	Total errors (adjusted)		31.4 (28.5)	28.1 (31.7)	0.06	
	Pre-EDS errors		9.2 (6)	8.4 (5.5)	0.15	
	EDS errors		10.7 (10.8)	9.1 (9.8)	0.3	
	Total number of trials completed on all attempted stages (adjusted)		107.6 (49.3)	101.79 (56.5)	0.08	
Working memory and strategy use	Spatial Working Memory					
	Number of between search errors for 8 boxes		16.4 (11.8)	13.9 (11)	0.11	
	Strategy score *(higher score = poor use of strategy)*	1-37	31.8 (5.2)	32.2 (5.1)	0.6	
Spatial planning and motor control	Stockings of Cambridge					
	Mean initial thinking time for 5 moves		9758 (7634)	11352 (7750)	**0.04**	Faster
	Mean subsequent thinking time for 5 moves		662 (701)	715 (796)	0.7	
	Problems solved in minimum number of moves		9 (1.9)	9 (2)	0.7	
Working memory capacity	Spatial Span					
	Span length recalled	0-9	6.5 (1.5)	6.9 (1.3)	0.12	

Rule acquisition and attentional set-shifting ability: There was a trend for cases to commit more errors than controls on the set shifting task (P=0.06), which has been attributed to problems in cognitive flexibility (Elliott *et al.* 1995). However, no differences were found between cases and controls on pre-extradimensional errors, or extradimensional shift errors.

A trend was also noted for cases to require more total trials to complete all attempted stages than controls (P=0.08), although no differences were found on the number of stages completed with both groups successfully passing all stages.

Working memory and strategy use: No significant differences were found between cases and controls on the number of between-search errors committed at the most difficult level (8 boxes) on the Spatial Working Memory task. No differences were also noted on the Strategy score of the Spatial Working Memory test with cases and controls equally efficient in their ability to adopt a systematic searching approach.

Spatial planning and motor control: Cases were significantly faster than controls in initial thinking time for five move problems (the most difficult level) on the Stockings of Cambridge planning ability task. The speed at which they made their decisions did not compromise their accuracy of the problems solved in the minimum number of moves.

Working memory capacity: Cases did not differ from controls in the length of spatial memory span on the Spatial Span test.

4.3.6.6 Visuospatial ability, verbal learning, non-strategic visual learning and memory and psychomotor speed /accuracy

The copy subtest of the Rey-Osterrieth Complex Figure Test (ROCF) (Osterrieth 1944;Rey 1941) was administered to assess visuospatial ability and perceptual organisation. The Rey Auditory Verbal Learning Test (RAVLT) (Rey 1941;Rey 1964;Taylor 1959) was administered to assess verbal learning and organisation. In order to assess psychomotor speed the Reaction Time task from the CANTAB (Sahakian and Owen 1992) was administered, measuring speed of response to a visual target where the stimulus is either predictable (simple reaction time) or unpredictable (choice reaction time). Five Choice reaction (latency to release the touch pad) and movement time (from release of touch pad to touch of the screen) is reported. (See Chapter 3 – Methods).

Data on cognitive tests of visuospatial ability, verbal learning, and psychomotor speed/accuracy are presented in Table 4.23. Data shown in this table are mean ± SD. Analyses were conducted using Independent *t*-tests. Wilcoxon-Mann-Whitney test was performed on data not normally distributed. Statistically significant p-values are in boldface.

Table 4.23 Subject scores on cognitive tests for visuospatial ability, verbal learning, and psychomotor speed /accuracy

Variable	Measure	Score Range	Cases N=101 Mean (SD)	Controls N=101 Mean (SD)	P value	Direction of Difference - cases compared to controls
Visuospatial Ability	**ROCF** Copy	0-36	30.4 (3.9)	31.4 (3.5)	0.10	
Verbal Learning	**RAVLT** Total Level of Learning (Trials 1-5)	0-75	53.4 (8.9)	54.1 (8)	0.6	
Psychomotor Speed/ Accuracy	**CANTAB** Reaction Time test					
	Five choice movement time in milliseconds		403 (113)	367 (101)	**0.02**	Slower
	Five choice reaction time in milliseconds)		352 (58.3)	343 (50)	0.2	

Visuospatial ability: No significant differences were found between cases and controls in visuospatial ability.

Verbal learning: No significant differences were observed between cases and controls in verbal learning ability with both groups achieving comparable number of words learnt over five trials of the RAVLT.

Psychomotor speed: Movement time for five possible different stimuli presented (the most difficult level) on the Reaction Time task was significantly longer in cases compared to controls. No group differences were found in reaction time.

There were no significant group differences in the number of tests failed, not completed or aborted on the CANTAB.

4.3.6.7 The effect of gender and age at baseline on neuropsychological results

Analysis of covariance (ANCOVA) was performed to examine the effect of gender and age at baseline (independent variables) on scores of neuropsychological measures (dependent variables) in cases (N=101). The variables of gender by age at baseline (that is, the interaction term), were also added.

Data on tests assessing intellectual ability, memory, attention, executive function, visuospatial ability, verbal learning and psychomotor speed are shown in Tables 4.24, 4.25 and 4.26.

Table 4.24 Effect of gender and age at baseline in cases (N=101) on tests assessing intellectual ability and memory

Variable	Measure	Significant effect	F value	P value	Interaction of gender by age at baseline
INTELLECTUAL ABILITY					
Pre-morbid estimate	**NART**	**Age**	**5.7**	**0.02**	NS
Current estimate	**WAIS-R**	**Age**	**11.9**	**0.001**	NS
MEMORY					
Verbal Memory					
Short-term	**RAVLT**				
	Immediate Memory Recall (Trial 1)			NS	NS
	Interference Trial (Trial 6 / List B)	**Age**	**8.7**	**0.004**	NS
Long-term	Delay trial (30 minutes)			NS	NS
Visual Memory					
Short-term	**CANTAB**				
	Delayed Matching to Sample				
	Mean latency time – all delays (milliseconds)			NS	NS
	Percentage of correct responses			NS	NS
	Spatial Recognition Memory				
	Percentage of correct responses			NS	NS
	Pattern Recognition Memory				
	Percentage of correct responses			NS	NS
Long-term	Paired Associates Learning				
	All stages completed %			NS	NS
	Total errors (adjusted)			NS	NS
	ROCF				
	Recall			NS	NS
	Recognition	**Gender**	**4.5**	**0.03**	**F=4.4; P =0.04**

Table 4.25 Effect of gender and age at baseline in cases (N=101) on tests assessing attention and executive function

Variable	Measure	Significant effect	F value	P value	Interaction of gender by age at baseline
ATTENTION					
Sustained Attention	**CANTAB**				
	Rapid Visual Information Processing				
	RVP 'A' Detecting sequences -			NS	NS
	RVP 'B' Tendency to respond regardless of whether target sequence is present	**Age**	**22.9**	**<0.0001**	NS
	Mean latency to respond (time in milliseconds)			NS	NS
Selective attention	Matching to Sample				
	Mean latency time (milliseconds)			NS	NS
	Percentage of correct responses	**Gender**	**8.8**	**0.004**	**F=7.5; P=0.01**
EXECUTIVE FUNCTION					
Rule acquisition and attentional set shifting	Intra/ Extra Dimensional Shift				
	Stages completed			NS	NS
	Total errors (adjusted)			NS	NS
Working memory and strategy use	Spatial Working Memory				
	Number of between search errors for 8 boxes	**Age**	**3.9**	**0.05**	**F=3.8; P=0.05**
	Strategy score			NS	NS
Spatial planning and motor control	Stockings of Cambridge				
	Mean initial thinking time for 5 moves			NS	NS
	Mean subsequent thinking time for 5 moves			NS	NS
	Problems solved in minimum number of moves (Planning ability)			NS	NS
Working memory capacity	Spatial Span				
	Span length recalled			NS	NS

Table 4.26 Effect of gender and age at baseline in cases (N=101) on tests assessing visuospatial ability, verbal learning and psychomotor speed

Variable	Measure	Significant effect	F value	P value	Interaction of gender by age at baseline
VISUOSPATIAL ABILITY	ROCF Copy			NS	NS
VERBAL LEARNING	RAVLT Total Level of Learning (Trials 1-5)			NS	NS
PSYCHOMOTOR SPEED / ACCURACY	CANTAB Reaction Time test Five choice movement time in milliseconds Five choice reaction time in milliseconds)			NS NS	NS NS

Effect of age

A significant main effect of age at baseline was observed on tests estimating intellectual ability, short-term verbal memory, spatial working memory and sustained attention.

Effect of gender

In addition, there was a significant effect of gender on tests assessing selective attention and long-term visual memory.

Effect of age and gender (Interaction)

The interaction of age at baseline and gender on tests assessing long-term visual memory, selective attention and spatial working memory was significant.

To assess if male and female MD survivors are differentially affected by the age at which they contract MD, regression analyses were computed to confirm the results from the ANCOVA and to take full advantage of all the variance in the age at baseline and gender variables. Each model included scores from the neuropsychological measures as dependent variables with gender and age at baseline again used as

independent variables. In addition, the interaction term (gender and age at baseline) was included in regression models.

Table 4.27 shows coefficients and 95% CI for the regression of neuropsychological test scores with gender and age at baseline.

Table 4.27 Table shows coefficients and 95% CI for the regression of neuropsychological test scores with gender and age at baseline. Cases only N=101

Variables	Premorbid Intellectual ability NART		Current estimate of intellectual ability WAIS-R		Short-term verbal memory Interference trial (RAVLT)		Long-term visual memory Recognition ROCF	
	Coefficient (95% CI)	p value	Coefficient (95% CI)	p value	Coefficient (95% CI)	p value	Coefficient (95% CI)	p value
Gender								
Male	0		0		0		0	
Female	7.0 (-44.7, 58.7)	0.80	15.4 (-40.1, 70.9)	0.58	-2.0 (-10.7, 6.8)	0.66	10.1 (0.66, 19.6)	**0.04**
Age at baseline	2.7 (0.56, 4.8)	**0.01**	2.4 (0.12, 4.7)	**0.04**	0.32 (-0.04, 0.68)	0.08	0.54 (0.15, 0.93)	**0.01**
Gender by age at baseline ℄	-0.32 (-3.2, 2.6)	0.83	-1.1 (-4.2, 2.1)	0.51	0.09 (-0.41, 0.58)	0.72	-0.57 (-1.1, -0.03)	**0.04**

℄ *Interaction term gender and age at baseline*

Table 4.27 (cont.) **Table shows coefficients and 95% CI for the regression of neuropsychological test scores with gender and age at baseline. Cases only N=101**

Variables	Sustained attention Rapid Visual Processing (RVP B')		Selective attention Matching To Sample (MTS) % of correct responses		Executive function Spatial Working Memory (SWM) (number of between search errors for 8 boxes	
	Coefficient (95% CI)	p value	Coefficient (95% CI)	p value	Coefficient (95% CI)	p value
Gender						
Male	0		0		0	
Female	0.00 (0.22, 0.22)	0.99	6.6 (2.2, 11.0)	**0.004**	-54.8 (-112.0, 2.4)	0.06
Age at baseline	0.02 (0.01, 0.02)	**0.001**	0.27 (0.09, 0.45)	**0.004**	-3.2 (-5.6, -0.84)	**0.01**
Gender by age at baseline (	-0.00 (-0.01, 0.01)	0.95	-0.34 (-0.59, -0.09)	**0.01**	3.2 (-0.04, 6.4)	**0.05**

(*Interaction term gender and age at baseline*

4.3.6.8 Effect of age and gender

The analyses revealed that at follow-up, survivors who were younger at MD, regardless of gender, performed worse on tests of intellectual ability (NART & WAIS-R) and on the test of sustained attention (RVP). In addition, male survivors who were younger at MD performed worse on tests assessing selective attention (MTS) and long-term visual memory (ROCF).

In contrast, survivors who were younger at MD committed fewer errors on the executive function task assessing Spatial Working Memory. There was no age or gender difference found in short-term verbal memory (RAVLT).

4.3.6.9 Summary of cognitive tests

No differences were found between survivors and controls in general intellectual ability and handedness. Survivors did however demonstrate problems in short-term verbal memory skills, cognitive flexibility and storage of verbal information. The ability to encode verbal material and retrieve it from long-term memory was unaffected. Impairment was also found in long-term visual memory. Significant deficits were also found in sustained and selective attention tasks. There was also some suggestion of minimal impairment in executive functioning, where survivors demonstrated a trend to commit more errors in attempting the attentional set-shifting task. MD survivors' also demonstrated significantly slower psychomotor speed compared to controls. However, survivors were not impaired in their response latencies on any other test in the battery. Furthermore, no impairment was observed on tests assessing visuospatial construction ability and visual recognition memory. Planning ability was also relatively well preserved. Survivors, younger at MD, performed worse on tests of intellectual ability and sustained attention (RVP) but committed fewer errors on the executive function task. Male survivors, younger at MD, performed worse on tests assessing selective attention and long-term visual memory.

4.4 Health professional follow-up

Data for follow up of cases by geographical region are shown in Table 4.28. Values shown are numbers and percentages.

Table 4.28 Follow up post-MD by region in the UK (cases n=101)

Region	Not followed up N (%)	Followed up N (%)	Total N (%)
North Thames	10 (53)	9 (47)	19 (100)
South Thames	14 (52)	13 (48)	27 (100)
Anglia & Oxford	6 (40)	9 (60)	15 (100)
South West	11 (44)	14 (56)	25 (100)
Trent	2 (33)	4 (67)	6 (100)
West Midlands	5 (56)	4 (44)	9 (100)
Total	**48 (48)**	**53 (52)**	**101 (100)**

Of the 101 cases, 53 had contact with a health professional post illness. The remainder reported that they had not even been seen by their general practitioner. There were no significant geographical variations in the proportion followed-up between regions ($p=0.92$, based on Fisher's exact test). Cases were not referred to a mental health professional at any time between the baseline study and the current study. None of the 20% of cases who were in the clinical range for depressive symptoms had received a referral to a mental health professional.

4.5 **Associations of identified deficits on functioning** (cases only)

In this section, the relationship of identified deficits with functioning in cases was examined. The ASBIR score and a cognitive summary score (CSS) were entered into multiple linear regression models as the independent variables with educational achievement (number of passes at GCSE and A level), mental health functioning (BDI-II and SF36 MCS), QOL, fatigue (Total Fatigue Score) and social support (SSQ6 Total score) as the dependent variables. The association of mental health functioning with cognitive performance was also assessed.

Adjustment of analyses for time between baseline and interview was undertaken in all regression analyses and made no material difference to findings.

4.5.1 Analyses of identified physical sequelae on functioning

The association of identified physical deficits with outcomes was examined. Coefficients and 95% CI for the regression of educational achievement, mental health functioning, QOL, fatigue and social support on ASBIR score are shown in Table 4.29. Coefficients are adjusted for age at follow-up and gender.

Table 4.29 Association of physical deficits (ASBIR score) with educational, psychological, quality of life, fatigue and social support measures

	ASBIR score	
	Adjusted coefficient (95% CI)	p
Number of passes at GCSE level	-0.01 (-1.06, 1.04)	0.9
Number of passes at A level	-0.48 (-0.98, 0.02)	0.06
BDI score	1.7 (-0.94, 4.3)	0.2
SF36 mental component score	-12.8 (-24.7, -0.98)	**0.03**
Quality of life compared with peers	-0.10 (-0.67, 0.45)	0.7
Fatigue score	1.5 (-0.33, 3.4)	0.11
Social support	0.01 (0.00, 0.01)	**0.04**

Poorer mental health functioning was associated with higher levels of physical sequelae. There was also a trend towards achievement of fewer A Level passes. A positive effect was that young people with physical sequelae had higher social support. Quality of life, fatigue or the number of passes at GCSE achieved were not associated with physical sequelae.

4.5.2 Analyses of the impact of identified cognitive deficits on functioning in cases

4.5.2.1 Cognitive Summary Score

In order to investigate potential mechanisms for poor QOL, fatigue, psychological and educational outcomes in survivors a Cognitive Summary Score (CSS) was derived. The CSS is a single variable comprised of scores for cognitive tests where cases had performed significantly worse than controls: short-term verbal memory (RAVLT, List B score), long-term visual memory (ROCF recall), sustained and selective attention (RVP A & MTS, mean latency) and psychomotor speed (RT, five choice movement time). The test raw scores were converted to z-scores using the mean and standard deviation of the control group for that test. The average of the five z-scores was calculated to create the summary score (CSS). Negative CSS scores indicate greater cognitive deficit compared with the controls, although the CSS was not used to differentiate between cases and controls. The mean for cases was -0.5 (SD 1.0). On tests where higher scores indicated impairment (for example timed tests), the z-score was inverted so that improved performance resulted in a higher CSS.

Previous investigators have used this method both in research (Brooks *et al.* 2000;Holthausen *et al.* 2001;Jung *et al.* 1999;Martis *et al.* 2003;Pugh *et al.* 2003;Sullivan *et al.* 2002;Travis *et al.* 2002;Wilson *et al.* 2000), and clinical settings (Spreen 1998). A single variable reduces the number of analyses conducted and Type I error.

To assess the impact of identified cognitive deficits on functioning in cases the CSS was entered as the independent variable into a multiple regression model and regressed against educational achievement (number of GCSEs and A Levels), mental

health functioning (scores from the BDI-II and SF36 MCS), quality of life, fatigue total score and social support total score (see Chapter 3 – Methods).

Associations of the CSS are shown in Table 4.30. The Table shows coefficients and 95% CI with coefficients adjusted for age at follow-up and gender.

Table 4.30 Associations of the cognitive summary score (CSS) with educational, psychological and quality of life measures

	Cognitive Summary Score (CSS)	
	Adjusted coefficient (95% CI)	P
Number of passes at GCSE level	0.90 (0.4, 1.4)	**0.001**
Number of passes at A level	0.30 (0, 0.6)	**0.05**
BDI score	-0.37 (-1.8, 1.1)	0.6
SF36 mental component score	2.5 (-4.2, 9.1)	0.5
Quality of life compared with peers	0.11 (-0.19, 0.42)	0.5
Fatigue score	0.40 (-0.62, 1.4)	0.5
Social support score	0.00 (-0.07, 0.08)	0.9

Greater cognitive deficit was associated with poorer educational achievement (fewer passes at GCSE and A level) but not with measures of mental health, quality of life, fatigue or social support.

4.5.3 Association of mental health functioning with cognitive performance

In order to investigate the association between mental health functioning and cognitive ability, the raw scores of each test were converted to *z*-scores using the mean and standard deviation of the control group. The average of the test z-scores was calculated to create the domain score used in regression analyses. Data are shown in Table 4.31. The Table shows coefficients and 95% CI. Coefficients are adjusted for age at testing and sex.

Table 4.31 Association of mental health function (cases only) and cognitive ability

	MENTAL HEALTH FUNCTIONING			
Cognitive domains	**Association with Depressive symptoms (BDI score) Adjusted coefficient* (95% CI)**	**P value**	**Association with SF-36 Mental Health Component score Adjusted coefficient* (95% CI)**	**P value**
Memory	-0.001 (-0.02, 0.01)	0.85	0.002 (-0.002, 0.01)	0.34
Attention	0.01 (-0.01, 0.22)	0.45	0 (-0.003, 0.04)	0.83
Executive function	0.01 (-0.01, 0.02)	0.39	0.001 (-0.002, 0.004)	0.64
Visuospatial ability	-0.003 (-0.04, 0.03)	0.88	-0.001 (-0.01, 0.01)	0.82
Psychomotor ability	0.013 (-0.02, 0.04)	0.40	-0.002 (-0.01, 0.01)	0.63
Non-strategic learning and memory	-0.01 (-0.02, 0.01)	0.31	0.001 (-0.002, 0.003)	0.56
Verbal learning	0.02 (-0.02, 0.05)	0.34	-0.001 (-0.01, 0.01)	0.87
Intellectual ability	0.001 (-0.03, 0.31)	0.94	0.001 (-0.01, 0.01)	0.75

Cognitive performance across each domain was not associated with the BDI and SF36 mental component score.

4.5.4 Association of premorbid IQ (NART score) with educational achievement and the cognitive summary score (CSS)

Association of premorbid IQ (NART score) with educational achievement and the cognitive summary score are shown in Table 4.32. The Table shows coefficients and 95% CI for the regression of premorbid intellectual ability with educational outcomes and the cognitive summary score. Coefficients are adjusted for age at testing and sex.

Lower premorbid intellectual ability predicted fewer exam passes at GSCE and A Levels, and a lower cognitive summary score.

Table 4.32 Association of premorbid intellectual ability with educational outcomes and the cognitive summary score (CSS)

PREMORBID IQ <100 vs. >=100			PREMORBID IQ <115 vs. >=115		
	Association with Premorbid IQ Adjusted coefficient* (95% CI)	P value		Association with Premorbid IQ Adjusted coefficient* (95% CI)	P value
Educational Achievement			**Educational Achievement**		
Number of passes at GCSE level			**Number of passes at GCSE level**		
Premorbid IQ <100	0		Premorbid IQ <115	0	
Premorbid IQ >=100	1.16 (0.13, 2.18)	**0.03**	Premorbid IQ >=115	1.83 (-0.40, 4.04)	0.11
Number of passes at A ' Level			**Number of passes at A ' Level**		
Premorbid IQ <100	0		Premorbid IQ <115	0	
Premorbid IQ >=100	1.06 (0.59, 1.52)	**<0.0001**	Premorbid IQ >=115	2.16 (1.15, 3.16)	**<0.0001**
Cognitive Summary Score (CSS)			**Cognitive Summary Score**		
Premorbid IQ <100	0		Premorbid IQ <115	0	
Premorbid IQ >=100	0.57 (0.23, 0.92)	**0.001**	Premorbid IQ >=115	1.03 (0.27, 1.80)	**0.01**

4.5.5 Relationship of mental health function and social support

Association of mental health functioning and social support are shown in Table 4.33. The Table shows coefficients and 95% CI for the regression of mental health scores (BDI and SF36 Mental Component Score) with the SSQ6 total social support score. Coefficients are adjusted for age at testing and sex.

Table 4.33 Relationship of mental health function and social support

	BDI		SF36 Mental Component Score	
	Adjusted coefficient (95% CI)	P	Adjusted coefficient (95% CI)	p
Social Support Total score	-0.05 (-0.08, -0.02)	**<0.01**	0.01 (0.01, 0.02)	**0.001**

Poorer mental health functioning was significantly associated with lower social support.

4.6 The number of cases scoring above or below the mean of controls in outcome domains

The number of cases scoring above and below the mean of controls in Physical function (Total Fatigue Score, General Health Perception); Quality of Life compared to before MD; Social Function (Total Social Support score); Academic achievement (number of GCSEs); Psychological function (Mental Component Summary score), and Cognitive Function (Cognitive Summary Score) is shown in Table 4.34.

Table 4.34 Cases scoring above and below the mean of controls

	PHYSICAL FUNCTION				QUALITY OF LIFE		SOCIAL FUNCTION		ACADEMIC ACHIEVEMENT		PSYCHOLOGICAL FUNCTION		COGNITIVE FUNCTION	
Cases Scoring Above or Below Mean of Controls	Total Fatigue Score		General Health Perception		QOL compared with before MD		Total Social Support Score		No. of GCSEs		Mental Component Summary Score		Cognitive Summary Score	
	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%
< mean	51	50.5	63	62.4	74	73.3	64	63.4	49	48.5	50	49.5	74	73.3
>= mean	50	49.5	38	37.6	27	26.7	37	36.6	52	51.5	51	50.5	27	26.7

Approximately half the cases scored above or equal to the mean of controls on the total fatigue score, number of GSCEs attained and the mental heath score. However, approximately one-third of cases scored above or equal to the mean of controls on general health perception and social support. Further, just over a quarter of cases scored above or equal to the mean of controls in respect to QOL compared with before MD and cognitive function.

4.7 Cases impaired in multiple domains

The number of domains affected in cases only is shown in Figure 4.2. Domain scores are < mean of controls on Total Fatigue Score, General Health Perception, Quality of Life compared to before MD, Social Function (Total Social Support score), Academic achievement (number of GCSEs), Psychological function (Mental Component Summary score), Cognitive Function (Cognitive Summary Score). In addition, the total ASBIR physical disability score (cases only) was included in these analyses.

Figure 4.2 Number of cases impaired in multiple domains

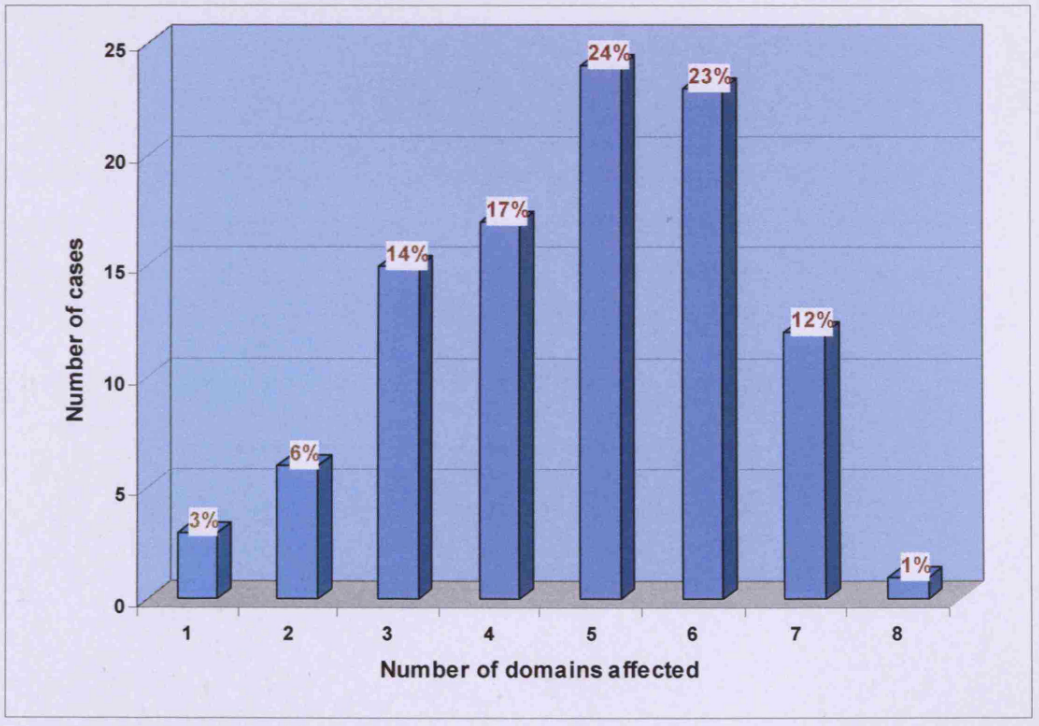


Figure 4.2 reports that all cases are impaired in at least one domain. Notably, only 3% of all cases were impaired in one domain whereas 47% of cases were impaired in five or six domains. One case was impaired in all eight domains.

4.8 Chapter summary

Survivors of MD in adolescence have greater mental fatigue, less social support, poorer educational outcomes and reduced quality of life 18-36 months after disease, compared with well-matched controls. These problems are in addition to deficits in short and long-term memory and attention as well as slowed psychomotor speed. Despite marked deficits, only half the sample was followed-up medically by any health professional including the participants' GP. A summary of significant cross-sectional findings of the data are presented in Table 4.35. Data shown in this table are mean ± SD unless otherwise stated on social support, quality of life, educational, health perception, fatigue and cognitive variables that are significant between cases and controls.

In addition, greater cognitive deficit was associated with poorer educational achievement (fewer passes at GCSE and A Level) not with measures of mental health or fatigue. In contrast, physical sequelae were associated both with poorer mental health functioning, as well as a trend towards poorer educational achievement (fewer A Level passes). However, physical sequelae were also associated with higher social support, while poorer mental health functioning was associated with lower social support.

Lastly, prior to adjustment for life stress, there was a trend for cases to have poorer mental health than controls, with lower mental health component SF36 scores being attained. Moreover, nearly twice as many cases as controls reporting depressive symptoms that were in the clinical range. After adjustment for life stress, cases were significantly more likely to have depressive symptoms than controls.

Table 4.35 Summary of significant cross-sectional findings between cases and controls

Measure	Variable	Score Range	Cases N=101	Controls N=101	P value
SOCIAL SUPPORT	Network score (average number of supports)	0-9	3.2 (1.4)	3.6 (1.3)	**0.03**
(SSQ6)	Total score	0-6	4.0 (1.1)	4.4 (0.9)	**0.01**
QUALITY OF LIFE	QOL compared with baseline median (range)	-5 to +5	-0.1 (-5 to 3)	0.96 (-3 to 3)	**<0.0001**
	QOL compared with peers mean (SD)		-0.80 (1.37)	-0.31 (1.26)	**<0.001**
EDUCATIONAL	Number of passes achieved at GCSE level: mean (SD)		8 (3)	9 (3)	**0.02**
	Percent who failed exams in the previous year		19	8	**0.04**
HEALTH PERCEPTION SF36-II	General health perception score	0-100	62.2 (20.4)	70.3 (18.8)	**<0.01**
FATIGUE	Mental fatigue score	0 – 12	4.6 (1.9)	4 (1.2)	**0.01**
Fatigue Scale	Poorer memory	0 – 3	1.0 (0.5)	0.9 (0.4)	**0.01**
	Making more slips of the tongue		1.2 (0.6)	1.0 (0.5)	**0.02**
	Total fatigue score (mental and physical fatigue combined score)	0 – 33	13.7 (5)	12.3 (4)	**0.04**
COGNITIVE					
Short term verbal memory -RAVLT	Interference Trial (Trial 6 / List B)	0-15	5.9 (1.8)	6.5 (1.7)	**0.04**
Long-term visual memory -CFT	Recall	0-36	16.6 (5.3)	18.6 (4.8)	**<0.01**
Sustained attention - CANTAB	Rapid Visual Processing (detecting sequences)	0-1	0.89 (0.05)	0.90 (0.05)	**0.01**
Selective attention	Simultaneous Matching to Sample (mean latency time, milliseconds)		1600 (479)	1460 (372)	**0.02**
Executive function	Stockings of Cambridge (mean initial thinking time for 5 moves)		9758 (7634)	11352 (7750)	**0.04**
Psychomotor Speed / Accuracy	Reaction Time Test (five choice movement, milliseconds)		403 (113)	367 (101)	**0.02**

CHAPTER 5 – RESULTS: LONGITUDINAL ANALYSES

5.1 Introduction

In this chapter, I examine longitudinal associations of baseline disease factors (four factors: seroGroup, age at MD, disease type [meningitis only, septicaemia only or mixed disease], and severity of MD [indicated by the number of days spent in intensive care]) with function at follow up. In addition, I investigate change over time in social support, stress and health behaviours in cases compared with controls from Time 1 (baseline) to Time 2 (follow-up).

5.2 Baseline disease factors

5.2.1 Physical sequelae

Sequelae were assessed on the Annotated Scale of Bodily Injuries Regulation (ASBIR), (Commission de la Santé et de la Sécurité du Travail 1987) a quantitative estimate of physical injury and disability (in cases), including anatomic and physiologic deficits, disfigurement and suffering or loss of enjoyment of life. Here I examine the distribution of individual sequelae by disease factors, as well as associations between disease factors and ASBIR score (see Chapter 3 – Methods).

5.2.1.1 Reported sequelae

Type of MD: Sequelae by type of MD are shown in Table 5.1. Of cases who reported physical symptoms (n=58) on the ASBIR, 16 (28%) had meningitis only; 16 (28%) septicaemia and 26 (45%) presented with mixed disease. A number of cases had multiple sequelae.

SeroGroup: The types of physical symptoms detected in seroGroups B and C are indicated in Table 5.2. In cases that reported physical symptoms and where data is available on seroGroup (n=46), 24 cases (52%) with seroGroup B had at least one

complication compared to 22 cases (48%) with seroGroup C. A number of cases had multiple sequelae.

Intensive Care Unit (ICU): The types of sequelae detected in cases admitted to ICU are shown in Table 5.2. Data were available on ICU admission in 97 cases; 52 (54%) were admitted to ICU (median number of nights in ICU, 2 nights; range 1 to 28). From the 52 cases who were admitted to ICU, (58%) n=30 had physical sequelae. A number of cases had multiple sequelae

Table 5.1 Number and type of physical symptoms reported on the ASBIR in cases by clinical presentation

	Clinical Presentation (N=58)			
Physical symptoms	**Meningitis N=16** **No. of symptoms reported**	**Septicaemia N=16** **No. of symptoms reported**	**Mixed Disease N=26** **No. of symptoms reported**	**Total number of reported symptoms**
Symptoms consistent with Raynaud's disease	6	9	13	**28**
Skin Scarring	0	6	12	**18**
Vertigo	5	3	9	**17**
Mobility problems	4	5	6	**13**
Speech problems	5	2	6	**13**
Hearing problems	5	2	5	**12**
Amputation(s)	0	1	2	**3**
Epileptic episodes	1	1	0	**2**
Impairment in upper limb function	0	1	3	**4**
Total number of symptoms	**26**	**30**	**54**	**110**

Note: Percentages in relation to the above data are not appropriate given that a number of cases had multiple physical sequelae.

Table 5.2 Number and type of physical symptoms reported on the ASBIR in cases by seroGroup and ICU admission

Physical Sequelae	SeroGroup B N=24 No. of symptoms reported	SeroGroup C N=22 No. of symptoms reported	ICU admission (N=30) No. of symptoms reported
Symptoms consistent with Raynaud's disease	12	8	15
Skin Scarring	6	10	16
Vertigo	7	6	9
Mobility problems	6	5	8
Speech problems	5	5	6
Hearing problems	8	1	3
Amputation(s)	0	3	3
Epileptic episodes	1	1	1
Impairment in upper limb function	1	3	4
Total number of symptoms	**46**	**42**	**65**

Note: Percentages in relation to the above data are not appropriate given that a number of cases had multiple physical sequelae

5.2.1.2 ASBIR score

Associations of disease and demographic characteristics at baseline with physical disability score (ASBIR) were examined using linear regression. Disease-related factors included MD seroGroup (C compared with B), type of MD (septicaemia or mixed septicaemia / meningitis compared with meningitis alone), severity of disease (number of days spent in Intensive Care Unit (ICU)) and age at MD and gender.

5.2.2 Factors associated with physical disability

Associations of disease and demographic characteristics at baseline with physical disability, at follow up are shown in Table 5.3. The Table shows scores for physical injury by baseline factor, coefficients, and 95% CI for the regression of ASBIR score on each of the baseline variables. Coefficients are adjusted for age at disease and gender. Statistically significant p-values are in boldface.

Table 5.3 Associations of disease and demographic characteristics at baseline with physical disability

Baseline factors	Total Physical Injuries score (ASBIR)		
	Mean (Range) ASBIR score	Coefficient (95% CI)	P
Disease type			
Meningitis alone	9.4 (1-76)	0	
Septicaemia alone	17.4 (1-238)	10.2 (-13.8, 34.2)	0.4
Mixed disease	22.2 (1-293)	12.4 (-8.8, 33.6)	0.2
SeroGroup			
B	18.8 (1-76)	0	
C	48.1 (1-293)	22.3 (2.2, 42.4)	**0.03**
Gender Male	27.9 (1-293)	0	
Female	30.2 (1-238)	-2.3 (-20.4, 15.7)	0.8
Age at disease	N/A	-4.2 (-10.3, 1.9)	0.2
Nights spent in intensive care	N/A	0.03 (-1.6, 1.6)	0.9

Greater physical disability was predicted by seroGroup C compared with B disease. The average physical impairment score on the ASBIR was higher for seroGroup C (48%) compared to seroGroup B (19%). Type and severity of MD, gender and age at disease were not associated with physical sequelae.

Where data is available on seroGroup, for cases admitted to ICU and who reported physical sequelae (n=30), the average impairment score on the ASBIR was 20% for serogroup B (n=10) and 60.4% for serogroup C (n=17).

For cases who were **NOT** admitted to ICU but reported physical sequelae (n=26) and where data is available on seroGroup, for seroGroup B (n=14) the average impairment score on the ASBIR was 18% compared to 6.4% for seroGroup C (n=5).

5.2.3 Factors associated with poor mental health

Associations of disease and demographic characteristics at baseline with mental health (Beck score (Beck 1987) at follow-up using linear regression are shown in Table 5.4. The Table shows the score for the Beck Depression Inventory (BDI-II) by baseline factor, coefficients, and 95% CI for the regression of BDI score on each of the baseline variables. Coefficients are shown adjusted for age at disease and gender. Statistically significant p-values are in boldface.

Table 5.4 Associations of disease and demographic characteristics at baseline with depressive symptoms

Baseline factors	Depressive symptoms (Beck Depression Inventory score)		
	Mean BDI score	Coefficient (95% CI)	p
Disease type			
Meningitis alone	7.2	0	
Septicaemia alone	9.0	0.8 (-2.7, 4.3)	0.7
Mixed disease	8.1	0.4 (-2.6, 3.5)	0.8
SeroGroup			
B	7.1	0	
C	7.3	-0.1 (-3.1, 2.8)	0.9
Gender Male	6.3	0	
Female	9.6	3.2 (0.63, 5.9)	**0.02**
Age at disease	N/A	-0.02 (-0.93, 0.89)	0.9
Nights spent in intensive care	N/A	-0.03 (-0.42, 0.36)	0.9

The BDI score was not associated with any disease factors. However, females were more likely to have more depressive symptoms.

5.2.4 Factors associated with fatigue

Associations of disease and demographic characteristics at baseline with the total fatigue score from the Chalder Fatigue Scale (Chalder *et al.* 1993) at follow-up using linear regression are shown in Table 5.5. The Table shows the total fatigue score for the Fatigue Scale by baseline factor, coefficients, and 95% CI for the regression of the

total fatigue on each of the baseline variables. Coefficients are shown adjusted for age at disease and gender. Statistically significant p-values are in boldface.

Table 5.5 Associations of disease and demographic characteristics at baseline with total fatigue score

Baseline factors	Total Fatigue Score (Chalder Fatigue Scale)		
	Mean fatigue total score	Coefficient (95% CI)	p
Disease type			
Meningitis alone	13.7	0	
Septicaemia alone	12.9	-1.3 (-3.7, 1.2)	0.3
Mixed disease	14.1	0.22 (-2.0, 2.4)	0.8
SeroGroup			
B	13.2	0	
C	13.1	-0.16 (-2.3, 2.0)	0.9
Gender Male	13.0	0	
Female	14.1	1.2 (-0.72, 3.0)	0.2
Age at disease	N/A	0.09 (-0.56, 0.73)	0.8
Nights spent in intensive care	N/A	-0.10 (-0.34, 0.22)	0.7

The total fatigue score was not associated with any disease factors.

5.2.5 Factors associated with cognitive deficit

Associations of disease and demographic characteristics at baseline with the cognitive summary score (CSS) at follow up using linear regression are shown in Table 5.6. The Table shows the CSS by baseline factor, coefficients, and 95% CI for the regression of the CSS on each of the baseline variables. Coefficients are shown adjusted for age at disease and gender. Statistically significant p-values are in boldface.

Table 5.6 Associations of disease and demographic characteristics at baseline with cognitive summary score (CSS)

Baseline factors	Cognitive Summary Score (CSS)		
	Mean CSS	Coefficient (95% CI)	p
Disease type			
Meningitis alone	-0.6	0	
Septicaemia alone	-0.5	0.21 (-0.28, 0.7)	0.4
Mixed disease	-0.5	0.18 (-0.25, 0.6)	0.4
SeroGroup			
B	-0.28	0	
C	-0.60	-0.24 (-0.65, 0.16)	0.2
Gender Male	-0.29	0	
Female	-0.75	-0.36 (-0.72, 0.01)	0.06
Age at disease	N/A	0.18 (0.05, 0.30)	**<0.01**
Nights spent in intensive care	N/A	0.02 (-0.03, 0.08)	0.4

The CSS was not associated with any disease factors. However, greater cognitive deficit was associated with being female and younger age at diagnosis.

5.2.6 Follow-up and Intensive Care

Associations of follow-up after MD with disease severity (ICU admission), physical sequelae (ASBIR score), social support, quality of life and mental health functioning (Beck 1987) are shown in Table 5.7. The Table shows scores for each outcome, coefficients, and 95% CI for the regression of follow-up post MD on physical disability, social support, quality of life and mental health functioning. Statistically significant p-values are in boldface.

Table 5.7 **Association of disease severity (ICU admission), physical sequelae, social support, quality of life and mental health functioning with follow-up**

Outcomes	Follow-up	
	Coefficient (95% CI)	p
Not admitted to ICU	0	
Admitted to ICU	0.24 (0.04, 0.43)	**0.02**
Physical sequelae (ASBIR score)	0.05 (-0.15, 0.25)	0.52
Social support (total) score	0.04 (-.06, 0.13)	0.45
Quality of life compared with baseline	-0.04 (-0.11, 0.03)	0.30
Mental health functioning (Beck score)	0 (-0.02, 0.02)	0.95

Those admitted to ICU were more likely to be followed-up after MD. However, follow-up was not associated with physical disability, social support, quality of life or mental health functioning.

5.3 Longitudinal differences between cases and controls in life stress and social support

This section examines whether cases and controls changed differently in life stress and social support from Time 1 (baseline) to Time 2 (follow-up).

5.3.1 Differences in Social Support

Associations of status, gender and age at follow-up with social support scores at follow-up adjusting for social support scores at baseline are shown in Table 5.8. The Table shows coefficients and 95% (CI) for the regression of social support scores (Network, Satisfaction and Total score) from the SSQ6 at follow-up on status, gender and age at follow-up, adjusting for baseline scores. Analyses were conducted using linear regression. Statistically significant p-values are in boldface.

Table 5.8 **Associations of status, gender, age at follow-up with social support scores at follow-up**

Coefficients adjusted for social support scores at baseline

	Association with Satisfaction with quality of support Coefficient (95% CI)	P value		Association with Social Network Score Coefficient (95% CI)	P value		Association with Total Support Coefficient (95% CI)	P value
Status			**Status**			**Status**		
Controls	0		Controls	0		Controls	0	
Cases	-0.19 (-0.42, 0.04)	0.1	Cases	-0.27 (-0.61, 0.07)	0.1	Cases	-0.20 (-0.44, 0.04)	0.1
Age at follow up	-0.02 (-0.10, 0.06)	0.6	**Age at follow up**	-0.02 (-0.13, 0.10)	0.8	**Age at follow up**	-0.01 (-0.10, 0.07)	0.7
Gender			**Gender**			**Gender**		
Male	0		Male	0		Male	0	
Female	0.27 (0.03, 0.50)	**0.03**	Female	0.07 (-0.28, 0.41)	0.7	Female	0.14 (-0.11, 0.38)	0.3

Social support scores for cases fell between baseline and follow-up after adjusting for baseline social support scores, but this failed to reach significance. Females were more likely to have higher satisfaction at follow-up regardless of MD.

5.3.2 Differences in life stress

Associations of status, gender and age at follow-up with stress and distress scores from the A-FILE at follow up adjusting for stress and distress scores at baseline are shown in Table 5.9. The Table shows coefficients and 95% CI-for the regression of stress and distress scores at follow up on status, gender and age at follow-up, adjusting for baseline scores. Analyses were conducted using linear regression.

Table 5.9 Associations of status, gender, age at follow up with stress and distress scores at follow up

Coefficients are adjusted for stress scores and distress scores at baseline

	Association with Stress Coefficient (95% CI)	P value		Association with Distress Coefficient (95% CI)	P value
Status			**Status**		
Controls	0		Controls	0	
Cases	-0.82 (-1.9, 0.3)	0.1	Cases	-4.1 (-10.9, 2.8)	0.2
Age at follow up	-0.20 (-0.6, 0.2)	0.3	**Age at follow up**	-0.70 (-3.1, 1.7)	0.5
Gender			**Gender**		
Male	0		Male	0	
Female	-0.72 (-1.9, 0.4)	0.2	Female	1.8 (-5.3, 8.9)	0.6

Stress and distress scores for cases fell between baseline and follow-up after adjusting for stress and distress at baseline, but failed to reach significance. Age and gender were not associated.

5.3.3 Differences in social and health behaviours

This section examines whether cases and controls changed differently in attendance of social and sporting activities, health risk behaviours and living arrangements from Time 1 (baseline) to Time 2 (follow-up).

5.3.3.1 Differences in attendance of social and sporting activities, health risk behaviours and living arrangements

Associations of status, gender and age at follow-up with attendance of social and sporting activities, health risk behaviours, and living arrangements at follow-up adjusting for social and sporting activities, health risk behaviours, and living arrangements at baseline are shown in Tables 5.10 to 5.12.

The Tables show coefficients and 95% CI for the regression of attendance at social activities (Table 5.10) and health risk behaviours and attendance of sporting activities (Table 5.11), and living arrangements (Table 5.12) at follow-up on status, gender and age at follow-up, adjusting for baseline scores. Analyses were conducted using linear regression. Statistically significant p-values are in boldface.

Table 5.10 **Associations of status, gender, age at follow up with attendance of social activities at follow up, coefficients adjusted for social activities at baseline**

	Association with Pub Attendance Coefficient (95% CI)	P value		Association with Nightclub Attendance Coefficient (95% CI)	P value		Association with Youth club Attendance Coefficient (95% CI)	P value		Association with Group Activities Coefficient (95% CI)	P value		Association with Religious Attendance Coefficient (95% CI)	P value
Status			**Status**			**Status**			**Status**			**Status**		
Controls	0		Controls	0		Controls	0		Controls	0		Controls	0	
Cases	0.02 (-0.07, 0.11)	0.6	Cases	-0.14 (-0.27, -0.02)	**0.03**	Cases	-0.04 (-0.08, -0.00)	**0.03**	Cases	-0.05 (-0.17, 0.08)	0.5	Cases	-0.02 (-0.10, 0.05)	0.6
Age at follow up	0.00 (-0.03, 0.03)	0.8	**Age at follow up**	0.01 (-0.04, 0.05)	0.8	**Age at follow up**	-0.01 (-0.03, -0.00)	**0.03**	**Age at follow up**	-0.04 (-0.10, 0.00)	0.06	**Age at follow up**	0.01 (-0.01, 0.04)	0.3
Gender			**Gender**			**Gender**			**Gender**			**Gender**		
Male	0		Male	0		Male	0		Male	0		Male	0	
Female	0.02 (-0.10, 0.11)	0.6	Female	-0.11 (-0.24, 0.02)	0.11	Female	-0.01 (-0.05, 0.03)	0.5	Female	0.06 (-0.07, 0.20)	0.4	Female	0.04 (-0.03, 0.11)	0.3

Table 5.11 Associations of status, gender, age at follow up with sporting activities and health risk behaviours at follow up, coefficients adjusted for sport attendance and health risk behaviours at baseline

	Association with Sport Attendance Coefficient (95% CI)	P value		Association with Smoking Status Coefficient (95% CI)	P value		Association with Regular use of recreational drugs Coefficient (95% CI)	P value		Association with Drinking Alcohol Coefficient (95% CI)	P value
Status			**Status**			**Status**			**Status**		
Controls	0		Controls	0		Controls	0		Controls	0	
Cases	0.04 (-0.10, 0.17)	0.6	Cases	-0.00 (-0.10, 0.10)	0.1	Cases	-0.08 (-0.17, 0.01)	0.09	Cases	-0.03 (-0.13, 0.10)	0.5
Age at follow up	-0.02 (-0.06, 0.03)	0.4	**Age at follow up**	-0.02 (-0.06, 0.01)	0.2	**Age at follow up**	-0.00 (-0.03, 0.03)	0.9	**Age at follow up**	0.02 (-0.02, 0.05)	0.4
Gender			**Gender**			**Gender**			**Gender**		
Male	0		Male	0		Male	0		Male	0	
Female	-0.24 (-0.38, -0.11)	**<0.0001**	Female	-0.05 (-0.15, 0.05)	0.4	Female	-0.13 (-0.23, -0.04)	**0.01**	Female	-0.01 (-0.11, 0.10)	0.9

Table 5.12 Associations of status, gender, and age at follow up with living arrangements at follow up, coefficients adjusted for living arrangements at baseline

	Association with Living with Family Coefficient (95% CI)	P value		Association with Living by self or with a partner Coefficient (95% CI)	P value		Association with Living with friend(s) Coefficient (95% CI)	P value
Status			**Status**			**Status**		
Controls	0		Controls	0		Controls	0	
Cases	0.10 (-0.10, 0.15)	0.3	Cases	-0.00 (-0.10, 0.10)	0.9	Cases	-0.05 (-0.14, 0.05)	0.3
Age at follow up	-0.10 (-0.12, -0.05)	**<0.001**	**Age at follow up**	0.04 (0.03, 0.06)	**0.001**	**Age at follow up**	0.04 (0.01, 0.10)	**0.01**
Gender			**Gender**			**Gender**		
Male	0		Male	0		Male	0	
Female	-0.01 (-0.12, 0.10)	0.8	Female	0.01 (-0.10, 0.10)	0.8	Female	-0.00 (-0.10, 0.10)	0.9

Social activities

Cases were significantly less likely to attend a nightclub or a youth club in the two weeks prior to interview at follow-up compared to controls, after adjusting for baseline attendance.

Age at follow-up predicted less attendance at youth clubs and group activities, after adjusting for baseline attendance, regardless of MD. Gender was not associated with social activities.

Health Risk Behaviours and Sporting Activities

Females were less likely to attend sporting activities or use recreational drugs on a regular basis at follow-up, when adjusting for baseline factors, regardless of MD. Cases at follow up were less likely to be regular users of recreational drugs, although this failed to reach significance (P=0.08). Age at follow-up was not associated with sporting activities and health risk behaviours when adjusting for baseline factors.

Living arrangements

Younger age at follow-up was associated with living at home with family and older age was associated with living alone or with a partner or friends, after adjusting for baseline factors, regardless of MD. Status and gender were not associated with living arrangements at follow-up, when adjusting for baseline factors.

5.4 Chapter summary

Greater physical disability was predicted by seroGroup C. Disease factors were not associated with fatigue and mental health functioning, although females were likely to have more depressive symptoms. The cognitive summary score was not associated with disease factors however, greater cognitive deficit was associated with being female and younger age at MD. Those admitted to ICU were more likely to be followed up after MD. Follow-up was not associated with physical disability, social support, QOL, or mental health functioning.

In assessing longitudinal differences between cases and controls from baseline to follow-up, it was found that social support scores and stress and distress scores fell between baseline and follow-up for cases, but they failed to reach significance, with females more satisfied with social support at follow up regardless of MD. In terms of longitudinal differences in social and health behaviours between cases and controls, the analyses revealed that cases were less likely to attend nightclubs or youth clubs, 2 weeks prior to follow up interview, and less likely to be regular users of recreational drugs, although this failed to reach significance. No further differences were found between the two groups.

SECTION D

CHAPTER 6 – DISCUSSION

6.1 Introduction

This is the first study to evaluate a comprehensive range of outcomes of MD in adolescents aged 15 to 19 years. Data were obtained from a population-based matched cohort. Survivors were followed prospectively 18 to 36 months after disease and compared with highly matched controls. As well as outcomes, demographic and disease factors associated with outcome were investigated. This study addressed an important and previously under explored area in medical research. The research conducted to date has shown that MD leaves a proportion of survivors with some degree of physical sequelae. However, studies vary widely in their methodological quality and the populations studied making it difficult to compare results.

Data revealed that adolescent survivors of MD have persisting physical, social, cognitive and psychological sequelae. Survivors were found to have greater depression, fatigue, less social support, poorer educational outcomes and reduced quality of life post MD, compared with well-matched controls. These problems are in addition to deficits in short and long-term memory and attention as well as slowed psychomotor speed. Those with seroGroup C disease had greater disease severity and physical disability. Key findings are shown in Table 6.1.

The adolescent years are marked by many psychosocial changes. When these changes are complicated by illness, the results can be highly problematic for many young people who survive MD. However, despite marked deficits, only half the sample had been followed-up medically post MD by any health professionals including the participants' GP. It is crucial that sequelae of MD are investigated in this age group, as these data show that the burden of continuing morbidity from MD in adolescence remains high. Careful follow-up of young people post MD is necessary to detect any problems they might be having and to facilitate their early resolution.

This section critically evaluates the methods used in the study and examines its findings in the light of published literature.

Table 6.1 Key findings of outcomes in MD survivors

Outcome	Findings	Level of Significance	CrossRef to sub-sections in Discussion
Survivors compared to controls			
Social Support	• Fewer people in social support network • Lower satisfaction with available support	*** ***	**6.3.1**
Mental health	• A trend for cases to have poorer Mental Health		**6.3.2**
Quality of life (QOL)	• Poorer QOL at follow-up compared to before MD • Poorer QOL compared to peers	* **	**6.3.3**
Physical	• Poorer General Health Perception • Greater total mental and physical fatigue • Higher mental fatigue	** *** ***	**6.3.4**
Education	• Fewer GCSEs achieved • Failed more exams in year prior to interview	*** ***	**6.3.5**
Cognitive	**Deficits found in:** • Short-term verbal memory • Long-term visual memory • Sustained attention • Selective attention • Psychomotor speed	 *** ** *** *** ***	**6.3.6**
In survivors separately			
	• Poorer mental health functioning is associated with greater physical disability	***	**6.3.2**
	• Greater physical disability is associated with higher social support	***	**6.3.4**
	• Cognitive deficit is associated with poorer educational achievement	**	**6.3.6**
	• Lower premorbid intellectual ability predicted fewer exam passes at GCSE • Lower premorbid intellectual ability predicted fewer exam passes at A level • Lower premorbid intellectual ability predicted greater cognitive deficit post-MD	*** * *	**6.3.6**
	• Poorer mental health functioning is associated with lower social support	**	**6.3.1**
	• Greater physical disability is associated with seroGroup C	***	**6.3.4**
	• Female survivors are more likely to have depressive symptoms	***	**6.3.2**
	• Cognitive deficit is associated with younger age at diagnosis	**	**6.3.6**
	• Survivors admitted to ICU are more likely to be followed-up	***	**6.3.7**
	• MD increases the risk of depression	***	**6.3.2**

*** <0.0001, ** <0.01, *** <0.05**

6.2 Methodological issues

Data were analysed from a matched group of survivors and controls initially recruited for a population-based case-control study investigating the risk and protective factors of MD. Case-control studies have been utilised extensively in epidemiologic investigations of disease aetiology and outcome with "informativeness" as their major strength (Breslow and Day 1983). When the aetiology of a disease is largely unknown, the case-control design can be extremely useful in providing information on a large number of risk factors for a disease. Whilst subjects were recruited and then followed up prospectively, it is acknowledged that case-control studies are susceptible to bias (Kelsey 1996) affecting the validity and generalisability of the findings (Sica 2006).

6.2.1 Causality

Many authors have discussed causality in epidemiology (Bradford-Hill 1965;Miettinen 1985;Rothman 1986;Schlesselman 1987) and all agree that 100% evidence for causality is impossible. The classic scientific technique often seen as the gold standard for establishing causality is the randomised controlled experiment (Harris *et al.* 2004).

However, epidemiology relies mostly on observational studies, such as the current study, where the group assignment is neither manipulated nor randomised and used primarily to uncover patterns and formulate hypotheses regarding the cause and effect of relationships (Greene 2000). One of the most difficult tasks in epidemiologic research is to assess whether associations between exposure and disease derived from observational epidemiological studies are of a causal nature or not (Rothman 1986). To draw sound inferences in observational studies requires identification of potential sources of bias and confounding. Many of the limitations in forming causal inferences from observational studies are due to three sources: uncontrolled confounding factors, selection bias and reverse causality (Greene 2000).

Confounding factors may either lead to spurious associations, where no causal relationship exists, or they may obscure a true causal relationship by producing an

association in the opposite direction. Statisticians have stated that regardless of how immaculate the study design is and how perfect the measurements are, it is virtually impossible to control completely for all confounders in observational data (Hernan 2006).

However, confounding variables can be adjusted for in statistical analysis. Such adjustments require careful consideration because in observational research, not all confounders are known by the researcher. Nevertheless, adjusting for confounders is a standard approach used in establishing causal effects in observational studies. In the current study, all regression analyses were adjusted for age and gender, as these have been strongly associated with many of the outcomes under study.

A number of epidemiologists have proposed guidelines for establishing inference of a causal relationship (Bradford-Hill 1965;Rothman 1986). The traditional approach and one that is commonly used is given by the British statistician Sir Austin Bradford Hill (Bradford-Hill 1965). Bradford-Hill suggested that a causal relationship might be inferred based on observational data through a number of criteria (see Table 6.2). He noted, "*All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge*" (Bradford-Hill 1965).

Table 6.2 Explanation of the Bradford Hill criteria for inferring causation when association is observed

*** Source:** (Holt and Peveler 2006)

One of Bradford-Hill's guidelines is *consistency of association.* This means that the greater the number of studies that observe a similar relation, preferably in different populations and perhaps with different study designs until all but the suspected cause can be ruled out, the more likely the association is causal. Based on this guideline alone causal inference cannot be drawn from the data collected cross-sectionally in the current study (self-report questionnaires as well as neuropsychological data). This does not allow determinations to be made about the directionality of relationships between variables as they are all measured at the same point in time, thereby limiting any conclusions that can only be tentatively accepted. Therefore, causal factors of group differences and their effects cannot be ascertained as conclusions cannot be drawn from a single study (Cox and Wermuth 2001).

In contrast, the longitudinal data collected in the current study at baseline and again at follow-up minimised some of the limitations of the cross-sectional data. It is generally accepted that longitudinal designs significantly enhance the interpretation of causality, and, specifically guard against the problems of reverse causation (Kessler 1987;Spector 1994). The longitudinal findings allowed for the assessment of the contribution of change and stability to be quantified between survivors and controls, establishing more clearly the temporal nature of the association, hence providing a much stronger basis upon which to infer causality. However, the observational nature of the study precludes definitive causal inferences.

In any investigation-assessing outcome, it is essential to reduce the effects of bias. Below, the potential sources of bias in this study are discussed together with the steps undertaken in the study to minimise their effect.

6.2.2 Potential sources of bias

Several potential sources of bias in this study fall into two main categories: selection bias and information bias. Particularly important is bias in subject selection (Schlesselman 1982) which is considered below.

6.2.2.1 Selection bias

Selection of controls is one of the most difficult and most heavily criticised aspects of case-control studies. Indeed, it has been suggested that the ideal control probably does not exist (Wacholder *et al.* 1992b). However, a crucial requirement is that the controls be comparable to the source population of the survivors (Olson *et al.* 2002;Wacholder *et al.* 1992a) as the most appropriate study sample is one that most closely reflects the characteristics of the population of interest (Sica 2006).

6.2.2.2 Sample bias

Prospective designs have been shown to minimise selection bias (Sica 2006). In this study, care was taken to minimise selection bias. MD survivors and controls were drawn from the baseline study prospectively recruited randomly from the general population from six regions of England.

Controls at baseline were recruited through the same general practice as the case, selected to serve as the normal population. Controls were individually drawn to optimally match each case based on several potentially confounding variables, sex, age and small geographical area of residence. The widely accepted strategy in the scientific community is to choose the most appropriate control group within the study context (Wacholder *et al.* 1992a).

A systemic disease such as MD is likely to have wide-ranging complications that will overlap with any number of conditions. Therefore, the choice of healthy controls was made in this study for comparative purposes in order to undertake a comprehensive evaluation of MD outcomes in survivors. As age, gender and socioeconomic status affect many of the outcomes under study, it was appropriate to match controls for these factors.

A valid set of controls was included in this study to test the hypothesis that survivors of MD in adolescence have poorer outcomes than in healthy age and sex-matched controls. However, in order to assess whether the outcomes reported in the current study are specific to adolescent MD survivors and not just the result of a life-threatening illness would require a different set of controls. For example, young people exposed to some form of extreme traumatic stressor such as admission to ICU

with an acute life-threatening event following injury, infection or cancer would enable comparisons of Post Traumatic Stress symptoms. Such symptoms have been found in adolescents and children undergoing cancer treatment (Nir 1985) and in children who have been exposed to other life threatening situations (Sturms *et al.* 2005). Other studies have reported similar findings in children and adolescents after unexpected and life-threatening incidents compared to chronic diseases such as diabetes (Bronner *et al.* 2008;Landolt *et al.* 2003;Murray *et al.* 2008;Yule *et al.* 2000). Indeed, to identify whether the outcomes reported in the current study are specific to MD survivors only, further studies could be undertaken in the future using specific control groups who would have experienced other life-threatening events.

Baseline study: With regard to case selection at baseline, it is acknowledged that the exclusion of a small number of survivors that died (16 survivors of 91 not recruited plus some of the 9 survivors recruited but not interviewed) biased the baseline study sample towards less severe survivors, although this was unavoidable. This was not an issue for the follow-up study of outcomes necessarily excluding death. Moreover, although at baseline 63% of recruited controls either were the first or second approached, 20% were the fourth or greater approached. This is a source of selection bias, as these secondary controls may well be different from those not willing to participate.

Follow-up study: From the 144 case-control pairs recruited at baseline (Tully *et al.* 2006) the first 115 pairs on the recruitment list were approached for follow-up in order to minimise selection bias and to correct for attrition. Four new controls were also recruited at follow-up to replace original controls that either refused participation at follow-up or could not take part for reasons outlined in Chapter 3 – Methods of this thesis. The four new controls were recruited through the general practitioner of the case and matched for age, gender, and place of residence. No differences were found in the four new controls compared to the original controls in terms of gender, ethnicity, age, occupation and socio-economic status, although the number is very small.

The follow-up sample did not differ from the baseline sample in terms of age, occupation, ethnicity, employment status, seroGroups, and type of MD. Also, both male and females were approximately equally represented (baseline, 51% male, follow-up, 46% male).

6.2.2.3 Loss to follow-up bias

Loss to follow-up in longitudinal studies is potentially a major threat to validity. This is mainly because if participants have moved or refuse to participate at follow-up, selective attrition may be a factor. This results in the research findings being compromised, threatening both the internal and external validity of the research (Flick 1988;MacMahon and Pugh 1970). Loss to follow-up rates of 30 to 40 percent can raise serious doubts about the validity of the study results in cohort studies (Hennekens and Buring 1987). In this study, the loss to follow-up rate was low with less than 10% of the total approached, refusing or unable to participate for reasons outlined in Section C – Results thereby, limiting the room for bias. At baseline, attrition was also low with only 4.5% of eligible case patients refusing participation (Tully *et al.* 2006).

To establish whether selective attrition may have been a source of bias in survivors and controls, lost to follow-up comparisons were made with those who were recruited at follow-up. No differences were found between survivors and controls recruited and not recruited in terms of gender, ethnicity, age and occupation. However, survivors who were approached but not recruited were slightly proportionally more likely to come from a lower social class (less home and car ownership) than survivors not recruited. This reflects the commonly seen tendency for those of lower socio-economic status to be more difficult to follow-up in research. This may have biased the study towards an under-estimate of the psychosocial sequelae of MD, (e.g. depression, low social support and stress), although it is unlikely to have affected longitudinal findings.

6.2.2.4 Observation (Information) bias

Observation or information bias results from differences in the methods in which information is collected from study subjects and may represent a threat to the validity

of a study (Szklo and Nieto 2000). Recall bias is a classic form of information bias (Grimes and Schulz 2002a).

Recall bias

Recall bias was minimised by gathering information using validated and reliable self-report questionnaires for mental and physical health, social support, stress, and fatigue and by applying standardised neuropsychological tests. The concept of measuring adolescent health through standardised self-report is well established (Starfield 1995). Young people were also asked about health risk behaviours, educational achievement and quality of life. Recall for these was minimised by using time-lines, (a short recall period of 2 weeks prior to interview regarding health risk behaviours), and memory aides such as calendars and personal diaries.

Nevertheless, it could be argued that survivors may have had a different attitude to the questionnaires than controls because of their previous illness and therefore it is acknowledged that measuring health on a range of self-report items is open to recall bias. However, firstly, this is unavoidable; secondly, validated instruments were used; and thirdly, differences based upon perceptions are actually key outcomes (e.g. depression, QOL, and social support).

There is always a risk that respondents do not correctly remember things that were asked for in a questionnaire. However, the main interest was in adolescents' experiences of MD during the past twelve months and daily functioning during the past two to four weeks. Moreover, at interview young people were encouraged to take their time to reflect before answering questions, and to think through the sequence of events that they were being asked about. Such techniques have been shown to reduce recall bias in surveys (Auriat 1993;Bradburn *et al.* 1987).

A further limitation is the use of proxies for disease severity (admission to ICU and number of days admitted to ICU) rather than a validated ICU score. Thus, the control for severity may have been suboptimal.

Interviewer bias

Blind assessment is the best way to ensure comparability of information in survivors and controls (Hennekens and Buring 1987). However, blinding was not possible in this study for two reasons. Firstly, given that some survivors had visible signs of disease (e.g. scarring or amputations), and as certain instruments were only completed by survivors, it was not possible to be blinded to case-control status of the subject. Secondly, as the researcher who managed the study on a day-to-day basis and the only researcher collecting data, I was aware of the main hypotheses under study. Accordingly, for practical reasons it was not possible to be blinded to the status of the subjects interviewed.

If blinding is not feasible it is recommended that standardised, uniform data collection procedures are used in all subjects (Kopec and Esdaile 1990). In this study, test instruments were standardised and validated where possible and standard data collection procedures were followed for all participants as recommended (Grimes and Schulz 2002a), resulting in minimal interviewer bias and greater reliability of the findings.

6.2.2.5 Generalisability

Generalisability, also called external validity or applicability is defined as the extent to which the findings obtained on a specific sample can be applied to the target population (Rothman and Greenland 1998).

The generalisability of the findings in the current study is strengthened by three principal factors. Firstly, validated measures were used and standardised data collection procedures were implemented. Secondly, recruitment of survivors and controls was population-based. Controls were selected from the general population and although the selection was not a random sample of the population that gave rise to the survivors, they were individually matched for age, gender and area of residence. The control subjects should be selected to be comparable to the survivors, and as a result will represent not the population of all non-diseased persons but the population of non-disease persons who would have been included as survivors had they

developed the disease (Hennekens and Buring 1987). It has been shown that population-based recruitment increases the generalisability or external validity of the findings of a study (Szklo 1998).

Thirdly, the success of longitudinal studies depends entirely on the sustained cooperation of its participants and generalisability to the target population depends on the study's participation rate for example, the percentage of sampled people who are willing to participate in the study (Van Ommeren 2003). In the current study participation was high, with less than 10 % of the total approached not participating. A minor limitation is that the most disadvantaged groups may be under-represented in this sample. However, low participation rates amongst poorer groups are common in epidemiological research (Smith *et al.* 2004).

The above demonstrates that the findings of the current study are highly generalisable to adolescents at least within the United Kingdom, and may be generalisable to other comparable industrialised countries.

6.2.2.6 Statistical significance and clinical relevance

This is the first detailed investigation of outcomes of MD in adolescence and it was hypothesised that there may be many areas in which deficits may be found. This resulted in administering a large number of measures, which was unavoidable in order to ascertain all potential outcomes. The comparison of cases with controls was therefore, based on multiple statistical tests thus inflating the risk of Type I error. Due to the descriptive and exploratory nature of the study the *post hoc* Bonferroni correction test (Bonferroni 1935) for multiple comparisons was not applied. It was felt that the application of the Bonferroni correction would inflate the probability of a Type II error. Therefore, significance levels are presented without correction with the conventional alpha level of .05 maintained for comparative purposes.

Power analysis was carried out *a priori* during the design stage of the study. Although there was sufficient power to examine the three hypotheses (as noted in the Methods Section), it was relatively underpowered overall due to the difficulty of recruiting sufficient survivors in a comparatively rare disease. Other outcome studies of MD

have also not corrected for multiple tests, possibly due to the same reason (Fellick *et al.* 2001;Moss 1982;Naess *et al.* 1994).

Bias due to multiple comparisons may have resulted in an overestimation of the significance of the results found and that some differences might reflect chance observations. The inferences that can be made based on the data are therefore limited by this lack of statistical power.

Accordingly, the approach adopted in this study was not to use a Bonferroni or other correction, as there are a number of issues that may be used to examine whether identified relationships are 'real' or not, of which significance is only one. For example, by examining whether the associations identified were biologically or psychologically plausible, whether there was a consistent pattern of deficits and whether the findings were consistent with clinical experience, patient perspective and previous publications can all be considered.

Some authors argue that the focus should not be on small P-values alone to make decisions about whether a study is useful and that clinical relevance is also essential (Javitt 1989;Sheps 1993). By focusing on the P-value exclusively can mistakenly classify clinically important effects as non-significant (Sterne and Davey 2001), and clinically important differences can be ignored. Alternatively, a significant P-value, in and of itself, may or may not be evidence of a clinically meaningful result.

The idea of significance testing was initially introduced by R A Fisher who argued that the P-value was an index measuring the strength of evidence against the null hypothesis. However, he also wrote that this fixed level of significance was "absurdly academic" and that it should be flexible based on the evidence and that interpretation of the P-value was ultimately for the researcher (Fisher 1950).

By reducing the level of significance associated with each test, one can reduce the power of the test, thereby increasing the chance of incorrectly keeping the null hypothesis or increasing chance of a Type II error (Kramer 1988). Real differences can be missed by merely focusing on the P-values. Statistically non-significant results can sometimes be highly significant clinically.

Bonferroni correction concerns an issue about which there is much ongoing debate in the biostatistical and epidemiologic literature and not wholly accepted for a number of reasons (Perneger 1998). The main argument centres around concerns when (if ever) adjustment for multiple testing is warranted (Aiken and Gensler 1996). Some authors have pointed out that this method of controlling Type I error comes at a cost. It leads to less sensitive comparisons and is perhaps too conservative, when the number of comparisons grows large and true associations are masked (Aiken and Gensler 1996;Jaccard and Wan 1996).

Perneger (1998) in the British Medical Journal makes the important point that '*there is an important difference between what the data say and what the researcher believes to be true*'. The latter depends not only on statistical significance but also on biological significance (Perneger 1998). Indeed the "*absence of evidence is not evidence of absence*" (Altman and Bland 1995).

In an explorative approach as undertaken by this study, the risk of inference errors should be balanced against the possibility that more accentuated group differences would have appeared had the study group been larger. The findings of the current study are clinically relevant. In general, knowledge about complications of MD in adolescence could be useful in clinical practice because it enables health care providers to support young people and develop coordinated services to ultimately improve young people's quality of life post MD.

Strengths

In addition to the measures taken to minimise bias, discussed previously, the strengths of the study include its prospective design, population-based recruitment of highly matched case-control pairs, the narrow age range of participants, data collected by one researcher and the use of a comprehensive protocol using standardised and validated measurements for assessing outcomes. An additional strength of this study includes the large numbers of survivors affected by different seroGroups with varying levels of disease severity and type.

6.3 Sequelae of MD

Few published data are available on outcomes of MD in adolescents other than physical disability. The majority of studies have examined outcomes of bacterial meningitis of all causes, on a very wide age-range, or in much younger children (Baraff *et al.* 1993).

6.3.1 Social outcomes

Self-report measures used to collect information on social functioning in participants included the Social Support Questionnaire (SSQ6) (Sarason *et al.* 1987) and elements of a questionnaire developed for the baseline study (previously modified from the West Country Meningitis Study [Stanwell-Smith, personal communication]) to assess social functioning and health risk behaviours. For the latter measure, a short recall period of 2 weeks was used as it was deemed more likely that adolescents would remember habitual behaviours and events within such a short time span. One limitation of self-report measures is bias. For example, social desirability bias refers to the tendency to answer self-report items in such a way as to deliberately or unconsciously represent oneself in a favourable light (Edwards 1953). Further, survivors may have had a different attitude to the questionnaires than controls because of their previous illness.

6.3.1.1 Social support

Findings: MD survivors at follow-up identified significantly fewer people within their social network on whom they could rely for support than controls. Survivors were also less satisfied with the quality of support available to them. When stratifying by gender, this was observed more specifically in male survivors rather than female survivors.

In terms of longitudinal change in social support network and satisfaction scores between baseline and follow-up, scores fell for survivors compared to controls but this failed to reach significance. Females were more likely to have higher satisfaction with support scores at follow-up than males regardless of MD.

Further exploration of social support in survivors found that poorer mental health functioning was associated with lower social support. One somewhat surprising finding was that young people with physical sequelae had higher social support scores.

Comparisons with the literature: This is the first controlled study to have assessed levels of social support after MD in adolescence and it is thus difficult to make comparisons. Social support is a widely used concept in the field of mental health, as well as in medicine and the social sciences (Sarason *et al.* 1990). It is a multidimensional construct and has been shown to have two basic elements: (a) the perception that there is a sufficient number of others to whom one can turn in times of need; and (b) a degree of satisfaction with the available support (Sarason *et al.* 1983).

Social support has been shown to be an important component in the recovery process after illness such as cancer, which can be influenced significantly by a person's access to supportive others (Henderson *et al.* 1981;Nuckolls *et al.* 1972;Sosa *et al.* 1980). Smaller social support networks are associated with poorer health outcomes after illness (Berkman 1995;Cohen 1992).

Social support systems may act indirectly on physical health by easing emotional or physical symptoms of illness (Wills and Cleary 1996), providing a sense of well-being, serving as a source of information and acting as a form of coping (Thoits, 1986), and enhancing self-esteem (Bowling, 1991; Weber, 1998). People comprising a social support network can help provide solutions to problems, provide comfort and the opportunity to listen and validate one's feelings (Cauce *et al.* 1996).

Support for the argument that social support protects against illness comes from epidemiological studies, however, these studies have rarely considered satisfaction with social support. Therefore asking adolescent MD survivors how satisfied they are with available support in the current study provides new important data.

Academic achievement in adolescents has been shown to be affected negatively with low social support (Barone *et al.* 1998;Garnefski and Diekstra 1996;Richman *et al.* 1998). In this the current study, survivors achieved fewer GCSEs and A Levels than

controls and poorer social support was associated with poorer educational achievement.

Low rates of social support are related to increased levels of depressive symptoms and anxiety in adolescence (Barrera and Garrison-Jones 1992;Demeray and Malecki 2002;Kaltiala-Heino *et al.* 2001;Mazza and Reynolds 1998;Paykel 1994). In the current study, it was found that survivors have a higher risk of depression and poor mental health function.

Low social support has been associated with difficulty in focusing attention on a particular task, and specifically on demanding tasks as well as increased levels of cognitive interference (Sarason *et al.* 1983). In the current study, while deficits in selective and sustained attention were found in MD adolescent survivors, social support was not associated with cognitive function.

The findings in this study are comparable with other published findings with regard to gender differences in social support (Geckova *et al.* 2003;Mazza and Reynolds 1998;Piko 1998;Vaux 1985). Females tend to report larger social networks than males and have been shown to be more able than males in seeking others for emotional support in stressful circumstances (Ashton and Fuehrer 1993;Seiffge-Krenke 1995;Taylor *et al.* 2000). This may be due to the fact that females normally have higher rates of self-disclosure with regards to feelings and problems than males and place greater emphasis on mutual support (Berndt 1982). Differences may also be explained by tendencies of females having better skills at identifying and/or engaging supportive persons, and having the ability to benefit from support (Vaux 1985).

There are a number of possible explanations for the lower social support reported by MD survivors. One explanation could be that an illness such as MD limits social activity after discharge due to physical complications and that low social support is a consequence of poor health status, possibly not having enough energy to socialise with friends or perform normal activities. The current study found that survivors were significantly more fatigued than controls. A second explanation is that they may also experience a swell of parental and peer support in hospital but upon discharge, peers may avoid them, as they may not know how to react if physical sequelae are severe. A third explanation is that survivors could also push away their social support system,

as they may cease to be interested in social activities and in maintaining friends, and may not have yet begun to come to terms with their own mortality.

Implications of the findings: The findings of poorer social support in adolescent MD survivors have a number of implications for further research, particularly developing strategies to identify factors that facilitate or hamper support post MD.

Social network analysis would be helpful in order to focus on a number of characteristics of the network, including not only size as in this study, but also composition and types of relationships as well as the perceived value or helpfulness of the support provided. Such analysis would determine the effectiveness of available support (Bowling, 1991). Research into these processes may assist in being able to clarify when and how to provide support for young people post MD. Young people value opportunities to express their feelings about their experience in a safe environment that encourages openness in communication and support, which can in turn serve to strengthen the young person and build resilience in dealing with the ensuing months after discharge from hospital (Greenberg 2006).

It is well known that young people are naturally resilient and able to cope with extremely difficult circumstances. This is supported by a recent qualitative study, which explored the psychosocial adjustment of the impact of meningococcal septicaemia in 11 survivors (aged 10-20 years at MD) who had MD up to five years previously (Wallace *et al.* 2007). The study found that participants demonstrated a high degree of resilience in response to their experiences of MD despite enduring serious after-effects. The study focused on their adjustment to appearance changes resulting from MD and concluded that overall the young people had come to accept their new appearance and had adapted satisfactorily. Interestingly, awareness of their close escape from death had been protective and facilitated adjustment to an altered appearance from scarring. Notwithstanding, participants had varied experiences of psychosocial support post-discharge from hospital, with some offered counselling whilst others left unsupported.

In the current study, despite the majority of cases affected in multiple domains of functioning some survivors were more resilient than others. For example, one young

man I visited (aged 17 yrs at interview) had bilateral amputations below the knee. He was cheerful through the interview and proceeded to show me his two new prostheses which he just recently had fitted followed by a tour of his newly adapted living quarters within the family home, with which he was very happy. His parents had also purchased a car for him, which was also adapted to accommodate his disability. He said that he had received tremendous support from the hospital and was followed up frequently in the ensuing months post-MD. Having the support of caring adults outside of family is an important contributor to resilience in young people (Blum 1998). This young man had clearly received support and guidance to adapt his life to his disability. Several years later I had to re-contacted him for another study and he informed me that he had "*recently moved in with his girlfriend*", indicating that he had clearly 'moved on' with his life. This implies that co-ordinated support after MD may be a potentially protective factor to adverse after-effects in adolescent survivors of MD, which in turn may enhance resilience.

In contrast, other adolescent survivors in the current study did not feel well supported following MD as demonstrated by the findings that social support was significantly lower in cases than controls with only 52% followed up by health professionals after MD. The role of support has been found to be a buffering or protective agent in alleviating the effects of stressful life events. For example, research in children surviving cancer has indicated that social support is positively related to children's level of adjustment to any after-effects (Neville 1998; Rait *et al.* 1992; Stern *et al.* 1993). Despite being naturally resilient, adolescents need support from health professionals and school following MD which may prove beneficial in their recovery, helping to mitigate the adverse effects of MD.

6.3.1.2 Social functioning and health behaviours

Social functioning

A knowledge of adolescents' leisure time and social activities and their interests are important for understanding the adolescents' social world and individual needs (Garton and Pratt 1987). Fulfilling social activities are considered to be important for healthy psychological development during adolescence (Hendry 1983). The current

study found no significant group differences at follow-up between MD survivors and controls in any measures of social function such as social activities, religious attendance, and leisure and sporting activities, with the exception of survivors attending fewer parties or nightclubs in the two weeks prior to interview compared to controls.

In assessing longitudinal change from baseline to follow-up, survivors were less likely to attend nightclubs or youth clubs compared to controls. Survivors were also less likely to use recreational drugs on a regular basis, although this failed to reach significance. With respect to age-appropriate independent tasks, survivors lived on their own at follow-up to an equal extent as did controls. This suggests that for survivors the experience of their illness had not hindered their progress towards a normally expected level of independence.

Research on social functioning post MD is scant. Only one previous study explores this issue. The findings of the current study are supported by a Canadian outcome study of MD survivors of all ages (which included a large sample of 10-19 year olds [n=231]) (Erickson and De Wals 1998). A reduction in leisure activities in MD survivors was found however, data were collected using an unvalidated postal questionnaire.

Health behaviours

Adolescents are typically regarded as an especially high-risk group for engaging in health compromising behaviours such as cigarette smoking and illicit dug use. These behaviours may place at risk the health of an individual in either the short or long term, and consequently they have been examined by several authors interested in adolescent behaviour (Jessor *et al.* 1980;Kann 2001).

In this current study, no differences were found between survivors and controls in reported health risk behaviours including smoking, alcohol consumption or drug use in the two weeks before interview. Further, MD status had no effect or change in health risk behaviour between baseline and follow-up.

6.3.2 Psychological complications

Four measures were used to assess psychological functioning in survivors and controls: the SF36 MCS, Beck Depression Inventory (BDI-II), the Clinical Outcomes in Routine Evaluation (CORE-OM) for assessment of mental health functioning and the A-FILE for the assessment of stress. All four measures have demonstrated high reliability and validity however, the possibility of self-report bias is acknowledged. Notwithstanding, self-report questionnaires are considered important in the assessment of depression, given the internal and subjective nature of the symptoms (e.g. feelings of guilt and hopelessness). Data on mental health functioning was collected cross-sectionally and accordingly, findings should be treated with caution. Data on stress were collected longitudinally (both at baseline and again at follow-up). All regression models were adjusted for age at follow-up and gender.

Findings on Mental Health Functioning: There were no significant differences between survivors and controls on the four dimensions of the CORE psychological scale. However, nearly twice as many survivors as controls (20% vs. 12%) reported depressive symptoms on the Beck in the clinical range, although this was not significant (P=0.1). However, MD increased the risk of depression significantly after adjustment for other known risk factors, including life stress, SES and gender. Further, there was a trend for survivors to have a lower score than controls (P=0.07) on the SF36 Mental Health Component Summary Score (MCS), denoting poorer mental health.

In survivors only, poorer mental functioning was associated with lower social support, higher levels of physical sequelae, and being female. However, poorer mental functioning was not associated with cognitive deficit.

Findings on Stress: At follow-up the total stress score on the A-FILE for survivors was significantly lower than controls, denoting less stress. This was an unexpected finding, and was explored further in order to assess if increased protection by the family and peers following MD had acted to reduce stressful events. Life events were divided into potentially controllable events (i.e. starting a new school or starting a new job) and largely uncontrollable life events (i.e. deaths, legal problems, and family

illness). Survivors reported fewer controllable events in the year preceding interview than controls at borderline significance (p=0.05) but not fewer uncontrollable events (p=0.07). This supports the hypothesis that survivors were exposed to fewer controllable events post MD. Stress and distress scores for survivors fell between baseline and follow-up, but failed to reach significance.

Low stress levels found in survivors could also suggest that post MD the focus of concern was on themselves and their own recovery rather than events within the family. It has been shown that difficulties experienced in the home situation are clearly important to the domain of adolescent stress (Call and Mortimer 2001) so it is surprising that survivors experienced less stress than controls. Furthermore, the stress finding may explain why in initial unadjusted analyses an association between MD and depression was not found.

Comparison with the literature: Depression is currently recognised as a significant health issue for adolescents due to its relatively high prevalence in the general population and the importance of stress in the understanding of adolescent health and well-being has been widely reported. Almost 30% of all adolescents will have experienced major depression by 19 years of age (Lewinsohn *et al.* 1998) with less than half ever seeking treatment (Ustun 2000).

Rates of depression and stress following MD in adolescents have not been formally measured in published studies. Only two studies have anecdotally examined psychological outcomes of MD.

A retrospective study examined anxiety post MD in survivors of all ages (including a large sample of 10-19 year olds, n=101) and found that 23% of 231 survivors reported increased anxiety at a mean of 38 months after the acute illness (Erickson and De Wals 1998). Despite using a self-administered non-validated postal questionnaire to assess anxiety, the finding from this study is important as anxiety can also be a symptom experienced by depressed young people (Puura *et al.* 1998).

In a more recent study, examining the complications of MD in 25 US college students (Erickson *et al.* 2001), the authors provided quotes from survivors regarding the

negative psychological impact that MD has had on their lives. For example, *"Psychologically, I find this disease hard to understand or accept"*, was recalled by one young man while a young woman said *"I just don't know why it happened to me...or why...I was under a psychiatrist's care for 6 weeks for depression"*. These are indeed useful insights into how young people feel post MD however mental health function was not formally assessed in this study.

Experiencing the perceived and real losses that have resulted from MD (e.g. loss of future and career aspirations) in some survivors as recalled in the study on US students (Erickson *et al.* 2001) can result in feeling isolated and lonely. In the current study, poorer mental health functioning was associated with lower social support. Some people will be supportive, other people will not, and some may simply avoid survivors resulting in feelings of sadness, anger and anxiety. There may be feelings of grief or feelings about the loss of the normalcy of adolescence.

If physical sequelae are not visible and they appeared to have recovered, survivors are often expected to catch up and keep up with their school or college work if they are in education or maintain a normal level of performance at work. Adolescents who are depressed are less likely to complete education, and are more likely to experience stressful life events (Lewinsohn *et al.* 1994).

Anniversaries of important dates, such as the date of diagnosis, could possibly bring on a variety of emotions, including relief, sadness, painful memories, or a combination of such feelings. A number of young people whom I interviewed stated that they felt *"anxious and down"* when the anniversary of their illness came around each year.

Alternatively, survivors may feel "invincible" and believe that since they survived MD, they can survive anything, which may lead to the development of unhealthy or risky behaviours, although an increase in health risk behaviours in survivors compared to controls was not found in the current study. A number of young people I had interviewed however started to pursue high-risk sports as they said *"I need to live for today, you never know what can happen in the future"*.

Other survivors may feel especially vulnerable because of the experiences they have had. Coming to terms with a traumatic event such as MD is hard to do at any age but in adolescence, it is potentially more burdensome. It can take months to recover from MD. Young people who have suffered such a life threatening illness, as MD may also fear and worry about the recurrence of infection and subsequent death. In the current study a number of young people said, they "*have times when they feel good and other times when they feel depressed and fear they are becoming ill again.*" Moreover, acquired physical impairment because of MD, even if relatively minor, could possibly have a major impact on the young person's self-worth leading to exclusion from activities. Accepting permanent disabilities coupled with the frustration of slow recovery could possibly be the reason for the presence of depressive symptomatology in some survivors. This is supported by the findings from the current study where poorer mental health functioning was associated with higher levels of physical sequelae.

Scarring from tissue damage in those that have experienced severe septicaemia may require skin grafts and it has been shown in adolescents that even minor disfigurement is a major problem for self-image (Kish and Lansdown 2000). At a time when most young people are concerned with appearance, wearing the right clothes, and adopting the latest hairstyles, young people post MD may become significantly concerned with complications, which in some survivors are very severe, such as amputation, extensive scarring and other disabilities. Being accepted and fitting-in is a significant concern for any young person but even more so for young people after MD.

Similarly, seizures, subtle visual problems, hearing loss or impairment, increased tiredness and amputation of digits (fingers or toes) or limbs due to septicaemia can have a material impact on young people's psychological, social and academic functioning, as well as on how they feel about themselves.

It is difficult to separate the normal difficulties experienced in adolescence from the sample in the current study as adolescence is a time of emotional turmoil.

Admission to Intensive Care can have far-reaching psychological effects. It has been reported in a British study that children (aged 2-15 years) treated on a Paediatric

Intensive Care Unit (PICU) and followed up 3-12 months post MD suffer post traumatic stress symptoms. In that uncontrolled study, 62% of children had symptoms of post-traumatic stress with 10% having the features of a stress disorder (Judge, et al. 2002). Without a control group, it is difficult to discern whether MD results in post-traumatic symptoms or is simply the consequence of a severe illness or ICU admission. Furthermore, the study only included children with severe illness that required PICU admission.

A meta-analysis identified a lack of social support after trauma as one of the major risk factors for Post Traumatic Stress Disorder (PTSD) (Brewin *et al.* 2000). PTSD is a constellation of psychological and physiologic symptoms that are persistent in some individuals who have been exposed to a traumatic event (Stuber and Shemesh 2006) and certainly contracting MD could constitute a traumatic experience. In this current study, PTSD diagnosis was not assessed but it was found that survivors had fewer social supports than controls.

Other studies have shown that life-threatening illness in adolescence such as cancer can precipitate symptoms of post-traumatic stress (Alter *et al.* 1996;Pelcovitz *et al.* 1996). Stressful events are thought to increase risk for a wide range of psychological problems among adolescents, including depression and anxiety (Johnson and Bradlyn 1988;Monroe and Peterman 1988).
In the current study, MD was negatively associated with stress and positively associated with depression which could be a psychological reaction to having experienced a life threatening illness or to being treated differently afterwards because of it. Depressive symptoms could also be triggered by any social problems that survivors may experience post MD, for example not being able to keep up with friends physically due to fatigue. In fact, a number of survivors I interviewed said that they often had to leave social gatherings early, as they felt exhausted very quickly.

It is unsurprising that in the current study it was found that poorer mental health functioning is associated with being female as it is well known that females generally record higher prevalence rates than males of both depressive symptomatology and diagnoses (Cohen *et al.* 1993).

Implications of the findings: An important finding is that MD increases the risk of depression in survivors post MD. Young people need to talk about their own reaction to the illness, their anxieties and fears for the future and possible depression and future hopes they may have lost (McCabe and Green 1987).

Support from others can help survivors cope with their emotions in a positive way. Charities such as the Meningitis Trust and Meningitis Research Foundation offer support with a Helpline open 24 hours a day led by nurses who are willing to listen and offer support and talk through any concerns. The Meningitis Trust also runs a free professional counselling service in the UK and Ireland to support sufferers and their families and anyone directly affected and can put the young MD survivors and their family in touch with support groups to help them come to terms with the experience.

The finding that MD increases the risk of depression in MD survivors in the current study demonstrates that young people post MD may need access to emotional and other types of support both at home and by health care professionals, as depression has been shown to have strong continuity into adulthood (Martin and Cohen 2000). Depressive symptomatology in adolescence can confer an increased risk for illness and interpersonal and psychosocial difficulties that persist (Weissman *et al.* 1999). One study found a direct linkage between early depressive symptomatology and increased risk of later major depression or anxiety disorders, nicotine dependence, alcohol abuse or dependence, suicide attempts, educational underachievement, unemployment, and early parenthood. These associations were similar for girls and boys (Fergusson and Woodward 2002).

6.3.3 Quality of life

Health related quality of life was measured with two instruments that assessed different aspects of participants' personal and social function and quality of life. No adequate scales cover the age range 15 to 19 years, so one validated adult-oriented scale (SF-36 II) was used and a simple unvalidated adolescent-oriented set of questions was formulated. Data on QOL were collected at follow-up only and accordingly it is not possible to state with precision whether poor QOL preceded MD or vice versa.

Findings: MD Survivors reported that overall quality of life (QOL) was significantly worse than their peers and unlike controls had not improved since the baseline study. Survivors also reported descriptively that home life, friendships, academic and vocational achievements, leisure activities, and physical ability have been affected since MD.

On the SF36, there was a trend (P=0.07) for cases to have a lower Mental Health Component Score (MCS) than controls, denoting problems in dimensions of mental health: role limitation with work or other daily activities due to emotional problems and social function and vitality. On the Physical Component Score (PCS) no significant differences were noted except general health perception which was significantly poorer in cases compared to controls. A single item of the SF36 related to change in subjects' health over the past year. This item is scored separately and is not included in the PCS or MCS scores. Forty-four percent of cases compared to 23% of controls reported that overall their health status had improved in the year preceding interview. QOL was not associated with physical sequelae or cognitive deficit.

QOL is increasingly acknowledged as an important health outcome measure in epidemiologic research. Subjective QOL among adults is thought to be generally stable on a population basis, while QOL has been found to be lower and unstable in adolescence (Petito and Cummins 2000). There is no consensus about the meaning of QOL and thus no generally accepted definition although it is accepted as a useful concept. Nevertheless, it is important to establish if QOL is affected post MD as adolescence and young adulthood are characterised by attempts to establish autonomy and independence, close personal relationships, educational goals and financial security. The additional impact of a life-threatening illness such as MD renders those tasks even more difficult.

Comparison with the literature: QOL post MD has been poorly studied in young people with just a handful of studies exploring this subject. Poorer QOL found in our survivors is supported by a Canadian study, which although it focused mainly on physical sequelae, also examined briefly QOL using an unvalidated postal questionnaire that included 12 statements concerning different aspects of QOL. An

overall impairment score was calculated providing an estimate of the magnitude of reduction of QOL. The study noted that 23% of 231 survivors reported poor QOL since MD (Erickson and De Wals 1998). It found that a number of different psychosocial factors compromised QOL, including reduced energy, increased anxiety, and a reduction in leisure activities and ability to work. Although these findings are useful, the authors did however pose QOL questions that were not specific to MD.

The same authors proceeded to examine outcomes of MD in 25 college students in the US (Erickson *et al.* 2001), using the EuroQOL EQ5D questionnaire (EuroQol Group. 1990) to evaluate QOL. This uncontrolled study found that 20% of these 25 young people reported a reduction in QOL compared to normative data. This reduction in QOL was primarily seen in those who had physical sequelae.

In contrast, a recent Dutch study assessed the outcomes of bacterial meningitis of all aetiologies and included a sample of 25 MD survivors (aged 15-60 years at illness) with good recovery and controls (Van De Beek D. *et al.* 2002). Subjects were followed up 6-24 months post-discharge. The RAND 36-Item Health survey (Ware and Sherbourne 1992) was administered to subjects to evaluate QOL and general health and included the same items as those in the SF-36 questionnaire used in the present study. MD survivors reported significantly lower energy levels in the Dutch study than controls, which is consistent with the findings of the current study.

The findings from the above studies provide support of reduced QOL following MD in young people however, none compared QOL in survivors with matched controls.

A Norwegian case-control outcome study of 71 young adult male survivors of MD noted that survivors anecdotally reported more general health complaints, including fatigue, increased irritability, poorer perceived memory and concentration, and a perceived reduction in work capacity compared to controls, and believed that MD had affected their educational success and vocational choices (Sander *et al.* 1984). Twenty-nine percent of the meningitis survivors and seventy percent of the septicemia survivors believed their vocational choice and educational success had been affected post MD.

Implications of the findings: These data suggest that poorer QOL occurs in MD survivors as previously reported. Specific instruments to measure QOL post MD in young people were not developed when this study was conducted. As a direct result of finding that adolescent survivors reported poorer QOL post MD we have undertaken a detailed study of QOL in MD survivors using validated generic instruments with the purpose of developing an MD-specific QOL (in preparation).

6.3.4 Physical health and injury

Findings:

Physical Injury: Fifty-seven percent of survivors reported physical sequelae ranging from minor skin scarring to bilateral amputations, with some young people suffering multiple sequelae. Hearing problems were reported in 12% of survivors. The most frequently reported physical injuries were symptoms consistent with Raynaud's disease, with nearly half reporting such problems, followed by skin scarring, with the least reported sequelae being epileptic episodes and amputation.

The majority of survivors reporting physical sequelae presented with mixed disease and MD caused by seroGroup B. However, the average impairment score was highest for survivors with seroGroup C. Over half of those reporting physical injuries, including amputees, were admitted to ICU and a higher number reported scarring and symptoms consistent with Raynaud's disease. Greater physical disability was predicted by seroGroup C. In addition, physical disability predicted fewer A Level passes although this failed to reach significance (P=0.06). Quality of life, fatigue or the number of passes at GCSE were not associated with physical sequelae. A positive effect was that physical sequelae predicted a higher social support score.

Physical Health and Fatigue: Survivors reported significantly poorer general health perception and greater fatigue compared to controls. More specifically, greater mental fatigue and problems in making more slips of the tongue, and poorer memory were noted. Despite these problems, more survivors reported that their overall health status had improved in the year prior to interview.

Limitations

Follow-up focused on neuropsychological, psychological and social outcomes, not on physical sequelae, which were assessed only by self-report. A clinical examination was not performed and injuries were not crosschecked with medical records.

As stated previously, self-report is susceptible to response bias, however this largely depends on the psychometric properties of the measures, in particular their reliability and validity (Nunnally and Berstein 1994). Both the SF36 and the Chalder Fatigue Scale are used to assess physical outcomes and have been used extensively in research and clinical settings and both have been found to be highly reliable and valid. The ASBIR has demonstrated similar validity, having been used to assess physical injury and disability in two previous studies of outcomes of MD in Canada and the United States (Erickson and De Wals 1998; Erickson *et al.* 2001).

Questions on physical injuries were asked in cases only by self-report using the ASBIR, and as stated above were not crosschecked with medical records. Therefore, the results reported here need to be seen in light of the lack of comparable data with healthy controls. This is important when considering the findings in cases where 28% reported symptoms consistent with Raynaud's disease, which are common symptoms in the general population (Wigley and Flavahan 1996). Such symptoms occur in up to 5% of a healthy population and predominately in young people less than 25 years of age (Isenberg and Black 1995).

A further limitation is that proxies were used for disease severity (admission to ICU and number of days spent in ICU) rather than a validated ICU score. Thus, the control for severity may have been sub-optimal.

Further, the sample in this follow-up study may be biased in favour of more severe disease and survivors from a lower socioeconomic group, as survivors recruited were proportionally more likely to have been admitted to ICU than survivors not approached for recruitment at follow-up. Notwithstanding, the ratio of sepsis and meningitis in this cohort [27% had septicaemia alone, 40% had mixed disease and 33% had meningitis] is similar to other outcome studies of MD. In a recent UK study (Fellick *et al.* 2001) 24% had septicaemia alone, 62% had mixed disease and 14% had

meningitis. The Canadian cohort of 452 survivors had 38% septicaemia, 47% mixed and 12% meningitis only (Erickson and De Wals 1998) with 3% unspecified; (the data for the current study and the Canadian data were both collected at times with high prevalence of a new clone of Group C meningococcus that was associated with higher rates of septicaemia). Lastly, there was less car and home ownership (i.e. lower socioeconomic status) in survivors who were approached for follow-up, but not recruited compared to survivors recruited for the current study.

Comparison with the literature

Physical Injury: The finding that greater physical sequelae was reported in survivors with seroGroup C disease is supported by a retrospective study of outcomes of MD in all ages in Canada (n=452) (Erickson and De Wals 1998). This Canadian study was the first study to examine the impact of MD using an objective physical injury scale - the ASBIR. Follow-up was at an average of 38 months after the acute illness. The study found the highest number of physical complications in adolescents and young adults with seroGroup C.

Higher proportions with physical sequelae in survivors with seroGroup C disease were also noted in a more recent retrospective study of MD amongst US college students (n=25) using the ASBIR. It found that 20% of survivors had permanent physical sequelae resulting from seroGroup C, mainly due to complications of septicaemia. No physical sequelae was noted in those with serogroup B disease (Erickson 2001).

The findings in this current study confirmed previous reports that significant physical sequelae are more common in adolescents than younger children. A study of 194 child survivors of MD (aged <18 years) conducted in the US, reported that only 5 (2.6%) had amputation or scarring (Wang *et al.* 2001) compared with 5% and 31% who had amputations and significant scarring respectively in the current series.

In the current study, 12% of survivors reported hearing problems that were assessed by self-report, which will likely under-estimate such problems. This finding is in contrast to the results of a Norwegian controlled outcome study of 71 young male MD

survivors (aged 18 and 24 years of age at MD), where only 7% reported reduced hearing (Sander *et al.* 1984), with no significant differences noted between survivors and controls. Sander et al, used both audiology assessment and a self-report questionnaire to assess hearing problems, which may explain the differences in results compared to the current study.

However, Naess et al examined survivors of MD of all ages one year after discharge from hospital and found that 19% of adults and 14% of children had some degree of sensorineural loss however no control group was used (Naess *et al.* 1994). Survivors had also undertaken an audiological examination.

One explanation for higher rates of physical sequelae found in adolescents in the current study compared to younger children is that the septicaemic form of the disease incurs greater physical damage (Erickson and De Wals 1998), and occurs with higher frequency during adolescence (Harrison *et al.* 2001). This is supported by the findings of the Canadian study (discussed above) where the majority of sequelae was secondary to septicaemia rather than meningitis (Erickson and De Wals 1998).

Physical Health and Fatigue: The finding that survivors perceive their health to be significantly poorer than controls and that they have greater fatigue is supported by the Norwegian study of 71 young male military recruits (Sander *et al.* 1984). This study noted that survivors anecdotally reported more general health complaints, including fatigue, than controls. It found that 13% had "relevant" complaints about their health deemed to be related to MD, whilst only 2% of controls had similar complaints. Such complaints included tinnitus, dizziness, visual disturbance, headache, irritability, sleeplessness and fatigue. The proportion of patients treated in ICU was not stated. Further, in the Canadian MD outcome study mentioned above, survivors reported reduced energy levels (Erickson and De Wals 1998).

A Dutch prospective study (Van De Beek *et al.* 2002) assessed the outcomes of bacterial meningitis of all aetiologies and included a sample of 25 MD survivors (aged 15-60 years at illness) with good recovery and controls. Subjects were followed up 6-24 months post-disease. Survivors reported significantly lower energy levels than controls, which is consistent the findings from the current study.

In contrast to studies reporting greater fatigue in female adolescents compared to males in the general population (Ghandour *et al.* 2004;Wolbeek *et al.* 2006), there were no gender differences found in the current study with both male and females reporting fatigue.

Fatigue can be difficult to define because it is loosely divided into physical and mental components and is a common complaint amongst adolescents for a number for reasons (hormonal, educational and social demands and psychological struggles) (Wolbeek *et al.* 2006). Moreover, fatigue is also a disabling consequence of many medical conditions for example, psychiatric disorders and syndromes of unknown aetiology, accounting for approximately 15% of medical care visits to infectious disease clinics (Carter *et al.* 1995).

There are a number of possible reasons why survivors in the current study reported greater fatigue than controls. For example, fatigue is a key symptom of depressive symptomatology (Nolen-Hoeksema and Girgus 1994;Wilson *et al.* 2005). In the current study, it was found that MD increases the risk of depression in adolescent survivors. Another possible reason for greater fatigue post MD in adolescent survivors is that an infectious illness, such as MD may play a role in the development of fatigue in some adolescents as part of an acute post-infectious fatigue syndrome. Fatigue has been shown to occur in later adolescence and young adulthood for example, after an acute febrile illness (Carter *et al.* 1995;Feder *et al.* 1994;Krilov *et al.* 1998;Smith *et al.* 1991). It has also been seen in young people after mononucleosis (usually caused by the Epstein-Barr virus, referred to as glandular fever) (Buchwald *et al.* 2000;Smith *et al.* 1991;White *et al.* 1998). This is interesting as more survivors than controls were positive for Epstein-Barr virus antiviral capsid antibody IgG (53% of survivors vs. 31% of controls) at baseline which has been linked to fatigue (Rea *et al.* 2001;Straus *et al.* 1985). However, in regression analyses performed in the current study no association was found with fatigue at follow-up (data not shown).

A positive finding from the current study is that more survivors than controls reported an improvement in their health status in the previous year prior to interview. No previous outcome studies have examined this subject. It is reasonable to suggest that although survivors experience physical sequelae, they may make a greater effort at

improving their health to combat the effects of MD, although they still perceive their general health to be poor.

Implications of the findings: Adolescence alone can be a stressful developmental process and a time of emotional and physical change. Fatigue and physical complications can potentially have negative educational, occupational, and social repercussions, which together could affect quality of daily life. However, in the current study physical disability was not associated with a reduction in QOL.

Illness in adolescence is a risk factor for the development of mental disorders in young people (Patel *et al.* 2007). In the current study physical disability post MD is associated with poorer mental health functioning. There are many possible reasons for this. For example, physical complications such as scarring and amputation could lead to body-image dissatisfaction and low self-esteem in young MD survivors, although self-esteem was not examined in survivors using an objective measure. Body image dissatisfaction in adolescence has been associated with depression (Ohring *et al.* 2002) and low self-esteem (Harter 1986;Rosenberg 1986).

A meta-analysis of 13 studies examining the effect of physical diability on self-esteem in young people found that young people with major physical disabilities are less affected compared to those with minor physical disabiliy (Miyahara and Piek 2006). This may be due to the high level of support that is provided to those with major physical disability, which is supported by the current findings as greater physical sequelae predicted a higher level of social support.

Nevertheless, the stigma of any disfigurement, especially when unrealistic images of 'attractiveness' exist across our society today, could potentially pose considerable challenges for young survivors in maintaining self-esteem, self-confidence and coping effectively with the possible negative reactions of others. Young people may feel uncomfortable with disfigurement in social situations; and find it hard to deal with comments and questions from other people. They might feel isolated or believe that they have little chance of leading a successful life. Counselling could be beneficial in assisting survivors deal with such problems and situations effectively.

The subjective report by survivors of mental fatigue, more specifically problems in memory, is confirmed by the findings from the objective neuropsychological tests, which demonstrated that survivors have deficits in short-term verbal and long-term visual memory. Mental fatigue refers to the effects that people may experience after or during prolonged periods of cognitive activity (Boksem *et al.* 2005). Furthermore, survivors also demonstrated deficits in attention (selective and sustained) and studies have shown that attention is specifically affected by mental fatigue (Bartlett 1943;Boksem *et al.* 2005;Brown 1994). However, in the current study the total fatigue (mental and physical) score was not associated with the cognitive summary score of deficit, which included attentional test scores.

The finding that physical disability was associated with fewer A Level passes (a trend, P=0.06) in MD survivors suggests that physical sequelae may be hampering educational progress by disrupting schooling. This may be particularly true for those young people with severe sequelae who would require ongoing treatment with visits to hospital or outpatient departments, thereby reducing attendance at school, which in turn would interfere with the preparation for and completion of exams. Survivors may be simply unable to attend school due to amputation or severe scarring, or may be psychologically unprepared to return to school due to disabilities, and lastly deafness has been reported to be a major cause of educational failure (Byrd 2005). A high rate (12%) of survivors in this study reported hearing problems.

6.3.5 Educational outcomes

In this study, young people were asked a series of short questions on educational achievement as part of the Questionnaire for Young People (previously modified from the West Country Meningitis Study [Stanwell-Smith, personal communication]). Educational achievement was assessed by the number of GCSE and A Level passes the young person had obtained, which are two crucial measures of educational attainment in Britain. Additional information included the number of days missed from education in the 3-month period before interview, exams failed in the year before interview and how participants rated their level of achievement during the school or college year subsequent to the MD. Data were collected cross-sectionally

and accordingly, findings should be treated with caution. All regression models were adjusted for age at follow-up and gender.

Findings: MD survivors achieved fewer passes at GCSE level compared to controls and were more likely to have failed an exam in the 12 months prior to interview. Of those who had completed their secondary education after the baseline study, 64% of survivors compared to 50% of controls did not attain any A Levels (P=0.07).

Greater cognitive deficit was associated with poorer educational achievement (fewer passes at GCSE and A Level) and there was a trend for physical sequelae to also be associated with poorer educational achievement (fewer A Level passes; P=0.06).

There were no differences between survivors and controls in the number of days missed from education, and work in the 3-month period preceding interview. More survivors rated their academic achievement at interview below average or average (75%) compared to 62% of controls, although this failed to reach significance.

Comparisons with the literature: I am unaware of studies that have formally assessed educational outcomes after MD in adolescence, although outcome studies of MD and bacterial meningitis of all causes have found poorer educational performance in younger children (Grimwood *et al.* 1995;Grimwood *et al.* 1996;Taylor *et al.* 1984) with persisting effects (Grimwood *et al.* 2000). In one study survivors of early childhood MD were approximately 3 times more likely to have a formal statement of special educational need (Fellick *et al.* 2001).

The finding that educational achievement was affected in MD survivors in the follow-up study is supported by a Norwegian case-control study (Sander *et al.* 1984) which examined outcomes in 71 male survivors of adult MD (aged 18-24 years at MD). However, standardised measures were not used and reliance was placed on the subjective experience of participants with 15% of survivors anecdotally reporting that educational plans had changed post MD and 7% stating the disease had influenced their choice of profession.

The fact that survivors are under-achieving academically is an important finding given the strong and well established association between school achievement and positive outcomes over the life span in terms of employment, occupational class, income, social exclusion and wider quality of life (Marsh 1990;Santrock 2002). This has important implications for MD survivors as self-esteem and academic achievement have been shown to be positively correlated: as self-esteem increases so does the level of academic achievement (Covington 1989;Schmidt and Padilla 2003).

The academic difficulties young people may experience post MD may be the result of a combination of factors. For example, well over half of all survivors reported physical sequelae, which was found to be associated with poorer educational achievement (trend) and poorer mental health functioning. Physical sequelae may inhibit a speedy recovery resulting in frequent absenteeism from school or college, contributing significantly to school under-performance and interference with the preparation for and completion of exams. As stated previously deafness has a major impact on academic success (Byrd 2005).

Poorer educational achievement has been linked to absenteeism from school in adolescents with chronic illness (Berg 1992;Breuner *et al.* 2004;van de Putte *et al.* 2005; Weitzman 1986).

Additionally, parents and teachers may alter their attitudes toward the young person because of the seriousness of MD, which may result in decreasing their academic expectations of the young person. Furthermore, it is possible that some survivors may be experiencing Post Traumatic Stress symptomatology as a result of MD, which has shown to have deleterious impact on academic achievement in adolescents (Saigh *et al.* 1997). In addition, greater fatigue was found in survivors compared to controls, which could have also contributed to poorer academic performance. However, the association of PTSD and fatigue in relation to educational achievement was not examined in this study.

Notwithstanding, no difference was found between survivors and controls for time taken off school in the 3 months prior to interview. However, this is a short time frame in which to deduce that absenteeism from education was not a problem.

However, cognitive deficit was found to be associated with poorer educational achievement in this study. Cognitive ability has long been strongly associated with educational attainment (Batty and Deary 2004;Deary *et al.* 2004). The presentation of cognitive deficits may not be immediately obvious to teachers and parents as the effects on learning may be subtle, manifesting as poor performance at school.

Implications of the findings: It is important that poorer educational achievement in young people post MD is identified. If it is not taken into account by teachers, the educational setting can potentially become a place of failure, both academically and socially, which may in turn strongly influence the young person's development of a sense of self-esteem, and his/her ability to perform and cope effectively after MD. There is also evidence that young people's desire to continue in further education is positively related to subsequent attainment at school (Ermisch and Francesconi 2001;O'Brien and Jones 2001). This is consistent with the findings of the current study as there was a trend for MD survivors to have fewer A Level passes than controls. Poor educational achievement in the long-term may impact on vocational choices and in turn loss of financial independence later in life.

Improving educational outcomes for young people post MD requires a multi-faceted approach that addresses the emotional and academic needs of the young person easing the transition back into education after MD. Providing a supportive educational setting coupled with teacher-support and medical support where necessary are essential elements to improve educational achievement in adolescent MD survivors. Survivors may benefit from individualised educational support from teachers to help them 'catch-up' with their peers when they return to school post MD as falling behind their peers may result in anxiety, placing additional strain on them, which may further interfere with their ability to concentrate and achieve academically or vocationally. The support of teachers has been found to be beneficial for adolescents returning to school after treatment with cancer (Klopovich *et al.* 1981). It is important that survivors do not feel isolated on their return to school. Research has shown that social support has positive effects on academic achievement (Vaux 1985). If physical sequelae are extensive, there may be ongoing medical treatments, which together with the resulting complications are constant reminders of their dependence on medical

support and their segregation from peers. Supportive friendships at school have been shown to have a positive effect on attitudes to school (Berndt 1996).

The results of this study also have implications for school counselling practice as MD survivors may benefit from one-to-one counselling to express and share their concerns.

These findings draw attention to the need for the provision of educational support for young people post MD. Without such support they may be rendered educationally disadvantaged which is likely to impact on their ability of finding suitable jobs and achieving financial independence as adults. It is incumbent upon teachers, school counsellors and medical health professionals to support survivors post MD and identify those with problems. The absence of support may leave survivors with diminished confidence in their ability to achieve future success.

6.3.6 Neuropsychological outcomes

An extensive neuropsychological test battery was administered to MD survivors and controls to examine a wide range of abilities. All tests used have demonstrated high reliability. Measures and procedures were standardised, thereby increasing the reliability of the findings. Adjustments were made in analyses for possible confounding variables such as age and gender.

However, it is important to note that the neuropsychological data are cross-sectional and any causal conclusions must be viewed with caution. In addition, bias due to multiple comparisons is possible. Adjustment for multiple significance testing could have been done by the Bonferroni method however, this was considered excessively conservative given the explorative nature of the study. Further, tests within each of the eight domains of cognitive functioning are closely correlated, for example, attentional mechanisms are not localised to specific brain regions (Scheibel and Scheibel 1958), and can be assumed to be more or less dependent on each other.

To reduce the number of statistical tests and avoid Type I error in investigating potential mechanisms for poor QOL, fatigue and psychological and educational

outcomes in survivors only, a Cognitive Summary Score (CSS) was derived to produce a single variable (see Chapter 3 – Methods).

Findings: The results demonstrate selective cognitive deficits in survivors not observed in matched controls. No differences were found between survivors and controls in general intellectual ability (premorbid and current estimates) with both groups falling in the normal range. Similarly, no differences between the two groups were noted with regards to handedness. Cognitive performance was not associated with scores on mental health measures.

The neuropsychological profile of MD survivors is one of diffuse impairment with deficits observed across a range of domains. Although, a generalised memory problem was not found, survivors did demonstrate problems in short-term verbal memory skills, cognitive flexibility and storage of verbal information. The ability to encode verbal material and retrieve it from long-term memory was unaffected. Impairment was also found in long-term visual memory, indicating a problem in recalling complex visual information from long-term storage.

Significant deficits were also found in sustained and selective attention tasks. There was also some suggestion of minimal impairment in executive functioning, where survivors demonstrated a trend (P=0.06) to commit more errors in attempting the attentional set-shifting task, which has been found to be attributed to problems in cognitive flexibility (Elliott *et al.* 1995). MD survivors also demonstrated significantly slower psychomotor speed compared to controls. Slowed psychomotor speed has been reported previously in patients sustaining mild (Katz and DeLuca 1992) and moderate to severe brain injury (Ponsford and Kinsella 1992).

However, survivors were not impaired in their response latencies on any other test in the battery. Furthermore, no impairment was observed on tests assessing visuospatial construction ability and visual recognition memory. Planning ability was also relatively well preserved.

The pattern of cognitive impairment found in survivors may essentially be due to slowed processing speed causing attentional problems, and memory dysfunction. For

example, slow processing may result in survivors failing to effectively organise and encode the Rey Osterrieth Complex Figure in time and store into long-term memory to facilitate later retrieval. Slow processing has been shown to often underlie attentional deficits (Gronwell and Wrightson 1981;Klove 1987).

Cognitive deficit (lower CSS) was associated with poorer educational achievement (fewer passes at GCSE and A Level), younger age at diagnosis and being female but not with quality of life, mental health functioning, fatigue, social support or any other disease factor.

In addition, higher educational achievement and premorbid IQ were found to play a protective role against greater cognitive deficit, indicating that survivors with higher cognitive reserve prior to MD experience less cognitive deficit post MD. This suggests that young people with higher premorbid IQ may represent a 'cognitively resilient' group. The factors underlying their cognitive resiliency remain unclear and further longitudinal research is required to assess if cognitive deficits persist and clarify the specific cognitive domains that are associated with poorer functional outcomes in MD survivors.

Cognitive reserve theory proposes that higher education and psychometric intelligence may preserve functional capacity following brain injury or disease, providing a buffer against brain dysfunction enabling individuals to compensate more effectively (Stern 2003). Support for cognitive reserve theory has been found in various conditions (Glatt *et al.* 1996) (Stern 2003). Further research is required to investigate the mechanisms that yield cognitive differences among survivors of MD and controls to improve understanding of the cognitive sequelae of MD in adolescence.

Screening young people post MD and assessing pre-morbid intellectual ability could be useful for identifying young people that are particularly vulnerable to cognitive deficit and therefore to target the necessary support.

Comparison with the literature: This is the first controlled study to specifically evaluate cognitive outcomes of MD in adolescence. Research is scant on cognitive outcomes of MD in all ages and the limited number of studies that have been

conducted have primarily focused on meningococcal meningitis in adults, including older adolescents in the sample. Therefore, a consistent and specific profile of neuropsychological abnormalities has not been established in adolescent survivors of MD. Accordingly, no direct comparisons can be made. More specifically, cognitive outcomes and the septicaemic form of MD have not been studied. Only three studies are relevant to this discussion.

Perhaps the most closely comparable data to support the findings in the current study are from a recently published Dutch study examining cognitive outcome in adults with good recovery after bacterial meningitis (Hoogman *et al.* 2007). This study included 76 adult survivors of meningococcal meningitis aged >16 years (mean age 38.9 years). Survivors were drawn from three long-term follow-up studies assessed 2-10 years post MD (mean 68.8, SD 49.4). The authors found significant deficits in survivors in short-term memory, attention, executive function and psychomotor speed. Being male was found to be a risk factor for cognitive impairment. These findings support the current study results, where a diffuse pattern of cognitive impairment was found with the same specific deficits. These findings are interesting although survivors with severe MD and septicaemia were not included. Further, controls were not randomly recruited but were mainly partners, relatives or close friends of the survivors.

The memory problems found in survivors in the current study is consistent with the findings from a Norwegian case-control outcome study of 71 young adult male MD survivors and matched controls. Although the study did not report specifically on the nature of neuropsychological disturbances, it found that 15% of survivors anecdotally reported impaired memory compared to controls (Sander *et al.* 1984) Unfortunately, standardised neuropsychological tests were not administered making comparison with the current study difficult.

The only other outcome study of MD that is relevant to this discussion assessed children and adults, including teenagers 1 year after the acute stage of MD (n=93, [52 adults and 41 children]) (Naess *et al.* 1994). This was a controlled study with only nine participants neuropsychologically assessed using the Halstead test battery. Only two patients were reported to have deficits (mild to severe), one of whom was a young

girl of 17 years with deficits found in attention and concentration. These findings are useful and comparable to the current study in terms of attentional deficits found in adolescent survivors however, the study sample is far too small for drawing meaningful conclusions.

Mechanisms: There are a number of possible mechanisms, by which MD might contribute to cognitive deficits. Attributing specific cognitive deficits in the presence of widespread disease is difficult. Furthermore, performance on any one measure typically reflects multiple underlying cognitive processes, and therefore it may be difficult to isolate specific mechanisms responsible for deficient performance in adolescents post MD. Nonetheless, advances in imaging technology are allowing researchers to construct a detailed picture of how the brain is affected by MD. For example, when meningococci bacteria access the central nervous system, their multiplication triggers a complex host response causing vasculitis and areas of infarction (Snyder *et al.* 1981). Generalised cerebral oedema is commonly found to occur in meningitis causing increased intracranial pressure (Ashwal *et al.* 1990) resulting in global and focal ischemic-hypoxic brain injury (Leib and Tauber 1999;Nau and Bruck 2002). The damage caused by MD at the acute stage of the illness may in part explain why a pattern of diffuse cognitive impairment was found in survivors in this current study.

The younger adolescents demonstrate a greater degree of deficit. This finding that younger age at MD was associated with greater cognitive deficit is consistent with brain biology. Recent research indicates that in contrast to previous assumptions, the brain continues to undergo a considerable amount of development throughout adolescence and into young adulthood. Research has found that during adolescence the refinement of neural circuitry occurs with changes in the volume of several brain regions, including the frontal and temporal cortex, amygdala and hippocampus (Giedd *et al.* 1996; Giedd *et al.* 1999; Giedd 2004; Sowell and Jernigan 1998). This increased plasticity of the brain during adolescence whilst facilitating learning, also appears to increase vulnerability to the damaging effects of acute infections such as MD and other illnesses. Studies have shown that subtle functions such as concentration, aspects of memory and attention remain sensitive to trauma beyond childhood (Christie *et al.* 1995). The pattern of diffuse damage found in MD survivors is

consistent with other infectious diseases that affect the brain for example, measles encephalitis or tuberculous meningitis (Berg 1989;Gelb 1990).

Implications of the findings: The findings suggest that adolescent MD survivors demonstrate deficits principally encompassing attention, mnemonic functions, and psychomotor retardation. The profile of deficits suggests it is consistent with diffuse brain damage (Lezak 1995).

In terms of practical implications, such deficits may affect aspects of daily life in adolescent survivors. For example, survivors with long-term visual problems may have difficulty with mathematics and geometric figures at school. In addition, survivors with such deficit may have difficulty in memorising geographical information such as charts and graphs.

Short-term memory problems may mean survivors have difficulty retaining information for a long enough time to manipulate it mentally. An example of this deficit might be the following: during a lesson or lecture at school or university, when a teacher states a key principle and then proceeds to give an illustrative example, the young person with a short-term memory deficit may lose track of the principle while listening to the example. The same thing may happen when reading, doing mathematical calculations or following directions.

Processing speed problems mean that young people may have difficulty understanding lengthy directions or lessons, completing reading or written assignments on time and completing any tests or assignments under timed condition, especially those involving extensive retrieval or organisation of information. Processing speed deficits may also impact negatively on other academic skills for mathematical calculations, and even tests or assignments, which are not timed. In daily life, depending on the severity of the processing speed deficit, there may be problems in taking phone messages, driving skills and any tasks involving rapid hand-eye coordination (e.g. sports, video games).

Attention problems manifest in difficulty focusing attention on a task when mental or physical distractions are present and competing for their attention. In school,

survivors would have difficulty attending to a lesson where there are environmental distractions. They may also find it difficult to apply themselves to school work for a long enough period to complete assignments well. In daily life, they may often be late and seem disorganised, inconsistent or unreliable. They may become very frustrated and tired due to the effort required to focus their attention. This is supported by survivors reporting significantly greater mental fatigue compared to controls.

Any of the above problems suggest that young people may benefit from cognitive rehabilitation post MD in order to improve their long-term outcome or from being taught compensatory strategies (e.g. audiotaping for note taking) for functional academic purposes. Therefore, screening young people post MD for cognitive impairment will identify those young people with deficits who may require support, particularly if severely affected. Cognitive rehabilitation has been demonstrated to be effective in reducing cognitive disability following brain injury (Laatsch *et al.* 2004;Pizzamiglio *et al.* 1998).

Rehabilitation may be more beneficial if it was integrated and coordinated with educational and vocational based support programmes. In particular, as young age at diagnosis was associated with greater cognitive deficit post MD, indicating that younger survivors may need more support, as they are more likely to be in full-time education. The fact that cognitive deficits persist long after the acute phase of the illness lends support for rehabilitation to extend beyond the immediate post-hospitalisation period as possible cognitive recovery is likely to evolve at a different pace for each young person.

In terms of the real-world impact of these deficits on everyday life, for a number of young people interviewed, memory and attention problems were reported to be a source of their frustration affecting their daily activities and in particular occupational and educational achievement. For example, I interviewed one young man who was in his first year at Oxford. Prior to MD, he was an excellent student who achieved high grades in most exams. However, post MD, he complained of memory and concentration problems and subsequently had difficulties maintaining the level of work required of the course. As a result, he started to fall behind and was eventually referred privately for neuropsychological assessment, which confirmed impairment in

aspects of his memory. At interview, he had undergone rehabilitation for several months and said that he had already seen some improvement. If support such as this was routinely offered to young people post MD, the long-term outcome may improve for those severely affected. Comments such as this, although anecdotal, correspond with objective data in this study of poor memory and attention problems.

6.3.7 Follow-up

Verification of medical follow-up was not undertaken in this study and the use of self-report data for medical follow-up may have led to an over or under-estimate of actual follow-up. However, recall of medical appointments after MD is likely to be high in this population with normal mean IQ and no deficits in long-term episodic memory. Further, subjective perception of follow-up is itself an important patient-centred measure of quality in health services (Cleary 2003). Data were collected cross-sectionally and accordingly, findings should be treated with caution.

Findings: Of the 101 survivors, only 53 reported contact with a health professional post illness. There were no significant geographical variations in the proportion followed-up between regions. Follow-up was predicted by disease severity, with those admitted to ICU more likely to be followed-up than survivors who were not. However, follow-up was not associated with the degree of physical disability, social support, quality of life or mental health functioning. MD survivors stated that they were not referred to a mental health professional at any time between the baseline study and the current study.

Of greater concern, two fifths of those admitted to intensive care did not receive continuing medical care and none of the 20% of survivors who were in the clinical range for depressive symptoms had been seen by their GP or received a referral to a mental health professional.

There is no national database that documents the use of outpatient services by patients after MD. Therefore, it is impossible to compare this cohort of adolescents with national follow-up rates after MD in patients of differing ages. Further, comparative data on health service use after meningococcal disease is not available. While follow-

up data were cross-sectional, it may suggest that follow-up, where it occurs, is not currently well targeted to those with the greatest deficit.

The current study was not set-up to examine whether follow-up improved outcome. This can introduce bias of course as those perceiving themselves as having problems are more likely to seek follow-up.

A number of survivors interviewed for the current study were found to have severe depression, in some cases suicidal ideation, which was ascertained by the Beck Depression Inventory. These survivors were encouraged to approach their GP for support and a number of organisations were recommended for additional help and assistance.

Currently there is no formal policy for follow-up in the UK for survivors of MD. While follow-up of younger children post MD by paediatricians has been reported to be routine, this was not found to be the case for the adolescents (survivors in this study). Many were discharged directly home from ICU by busy adult medical services. The dangers of poor services for adolescents at the intersection of paediatrics and adult medicine, and the importance of improving these transitions (Viner and Barker 2005) has been emphasised by the recent UK National Service Framework for Children and Young People (Department of Health 2004b). Classic paediatric or adult outpatient services often poorly serve young people with acute illnesses ignoring their unique developmental needs (Royal College of Paediatrics and Child Health 2003).

The need for better follow-up has also been emphasised by MD survivors. In a recently conducted study to develop a specific QOL questionnaire for young people post MD, I held focus groups with 16 – 24 year old survivors of MD during which participants stated that they wanted regular medical follow-up after discharge from hospital in order to monitor their emotional as well as physical health (unpublished data).

Routine follow up post MD in adolescent survivors is therefore essential for offering reassurance, monitoring the severity of late effects of MD and linking them in to other

services for example arranging hearing tests, eye tests, and visits to specialised clinics if necessary. GPs are best placed to offer support and initial screening and their service is not cost-prohibitive (£17.42 per visit) (DOH 2004) considering the long-term health and cost implications to the NHS and the individual if outcomes are not monitored. GPs may be more cost effective than attendance at an outpatient clinic, the costs of which are approximately £276 for a first visit to an Infectious Diseases Outpatient Department and approximately £190 for each appointment thereafter (DOH 2004).

Implications of the findings: Survivors of MD in adolescence have a disturbing series of deficits including significant fatigue, poorer quality of life, cognitive function and educational achievement compared to controls. Medical care is poor after discharge from hospital and routine follow up is important for preventing treatable morbidity after MD, which may go unrecognised and untreated in some survivors. Follow-up support services can help young people come to terms with their experience of a life-threatening illness and provide the opportunity for them to access further intervention if required. In addition, follow-up can ensure that the young person and their families are provided with accessible and realistic information, to help them gain an appropriate understanding of the illness and its possible effects. Health care providers therefore need to seek interventions at both the individual and policy level that address young people's needs post MD and enhance their quality of life.

The present study found that all cases were impaired in at least one domain of functioning post-MD. Nearly half of cases were impaired across multiple domains of functioning (social, psychological, cognitive, and physical function as well as QOL and academic achievement – with the principal domains affected being physical function, QOL and cognitive function). These findings, which were previously unknown, have important implications for clinicians and families in supporting adolescents post-MD. Firstly, they alert clinicians to potential adverse areas of function in adolescent MD survivors and will prompt them to further enquire with survivors and their families on areas of functioning such as social support, depression, memory problems, and disability, with a view to therapeutic intervention where possible. Secondly, clinicians can inform adolescent survivors and their families about the possible after-effects of MD, providing guidance on how to access comprehensive

follow-up care. Therefore, the findings of this study will guide clinicians in their assessment of young people post-MD, ultimately leading to better after-care, which in turn ensures an improvement in quality of life for adolescent MD survivors.

For survivors with severe after-effects, a more intensive, multidisciplinary approach may be required and it is important that service delivery is coordinated. For example, some young people may be unable to continue full-time work or education for some time with recovery disrupting school or university studies. A team approach accompanied by an understanding of how MD impairs the quality of life may improve the management of the adolescent's health problems post MD, both in health-care services and in educational institutions. Successful return to work or school requires a support programme, incorporating medical treatments, psychological support and occupational therapy for young people with severe complications. Prolonged absence from school may lead to anxiety about falling behind with class work, and young people may become frustrated and/ or anxious about their inability to participate in sporting and social activities if physical sequelae are severe. For survivors experiencing cognitive problems a referral to a clinical Neuropsychologist may be highly beneficial in order to identify appropriate educational support and identify potentially effective rehabilitation strategies.

For some young people post-MD joining a support group may be valuable. Charities can offer individual and group support, education on MD, and advice. Individuals may also benefit from the opportunity to exchange information on how to cope with the many practical day-to-day difficulties that arise for young people after MD.

A systemic disease such as MD is likely to have wide-ranging complications that will overlap with any number of conditions. Therefore, it is not possible to state with certainty if the range of outcomes found in adolescent survivors in the current study, are specific to MD. Further, this is the first study to explore outcomes in adolescent survivors so there are few comparisons.

However, the pattern of deficits found in survivors in the current study, more specifically physical injuries caused by sepsis and cognitive impairment are specific

to MD. The physical injuries reported in survivors in this study are consistent with the findings from other MD outcome studies which have included adolescents and young people (Erickson and De Wals 1998;Erickson *et al.* 2001). Both studies conclude that physical sequelae were primarily due to complications of meningococcal sepsis.

Meningococcal Sepsis may cause cerebral insult due to vasculitis and cerebral hypotension, the release of inflammatory factors within the brain, and the occurrence of small septic infarcts. Such damage may have resulted in the pattern of diffuse cognitive deficits found in this study, including deficits in attention, aspects of memory, cognitive flexibility, and psychomotor speed.

Certainly, compared to viral meningitis, which is rarely life-threatening, bacterial meningitis more specifically pneumococcal and meningococcal meningitis cause greater cognitive impairment (Schmidt *et al.* 2006). In survivors of pneumococcal meningitis cognitive deficits have been greater than those found in survivors of meningococcal meningitis (van de Beek *et al.* 2002). However, this study included adult MD survivors with good recovery and therefore comparisons cannot be made to adolescent MD survivors where the brain is still maturing and is more vulnerable to damage.

Other life-threatening illnesses may not cause the specific cognitive deficits as found in adolescent MD survivors in the current study. However, greater reduction in quality of life, poorer social support and lower educational attainment could potentially be outcomes of any life-threatening illness.

CHAPTER 7 – CONCLUSIONS AND FUTURE DIRECTIONS

This prospective population-based matched cohort study is the first to explore outcomes of MD in adolescent survivors. The study provides insight into the full extent of the sequelae among a representative sample of adolescent MD survivors, including a detailed and careful assessment of neuropsychological function. Few comparable data are available on outcomes other than physical disability.

7.1 Conclusions

The results show that 57% of cases had physical sequelae ranging from minor scarring to bilateral amputations. Survivors had greater mental fatigue, lower social support, greater reduction in quality of life, and lower educational attainment compared with controls. Cognitive testing revealed no overall change in intellectual ability; however, cases had deficits in aspects of memory (short and long-term), attention (selective and sustained), cognitive flexibility and psychomotor speed. Greater cognitive deficit was associated with a younger age at diagnosis. Cases with SeroGroup C disease had greater physical sequelae than those with B disease. MD status increased the risk of depression. Medical follow-up and educational support for cases was poor. Only 53/101 cases reported any medical follow-up after MD. I am not aware of comparative data on health service use after meningococcal disease. Furthermore, I found no associations between reported follow-up and the degree of physical deficit or other sequelae.

The mechanisms by which MD produces these adverse educational, cognitive, psychological and social outcomes is not well understood. Some deficits may directly result from central nervous system vascular damage or hypoperfusion during the acute illness (Pathan *et al.* 2003). Some deficits may be a more indirect consequence of psychological responses by the individual or their family to having a life-threatening illness (Benzer *et al.* 1983) to treatment in intensive care (Rees *et al.* 2004), or to ensuing physical disability (Erickson and De Wals 1998). The findings suggest that

poorer mental health functioning is related to the impact of physical complications after MD, and that poorer educational outcomes are related to cognitive deficits. However, these particular associations are cross-sectional and causality cannot be assumed. Whilst the impact of MD on cognitive function appears to be independent of mental health function, it has an impact on subsequent educational achievement.

The findings indicate that MD continues to impact upon the lives of adolescent survivors 18-36 months post-disease. The implications of the physical sequelae noted are significant. In particular, survivors with high rates of physical sequelae were more likely to have poorer mental health functioning. It is possible that the experience of physical sequelae by adolescent survivors would have interrupted progression in schooling.

The study noted that MD increased the risk of depression, and demonstrates that young people post-MD may need access to emotional and other types of support both at home and by health care professionals. Encouraging adolescents to share their concerns and discuss ways to help them cope with the effects of MD will assist them in their return to normal life and daily functioning and dispel any anxiety and uncertainty they may feel about the future after MD. Depression may be due to the difficulties found in achieving educationally and vocationally and by the fact, they feel under-supported or simply coming to terms with a life-threatening disease. The study also found that life stress levels were lower in survivors than controls. This finding was unexpected, and may reflect a reduction of exposure of cases to avoidable stress, by themselves or by their family, after MD.

Another important finding of the study is that MD leads to poorer quality of life. The implications of this, many of which are connected to other findings of the study as noted previously, are that a number of areas of the survivors' lives are impacted upon post MD. For example, survivors may feel that in addition to poorer educational achievement and less support, their general health overall was poor which may in turn impact on aspects of their lives. The implication of this is that it may exacerbate many of the effects discussed above.

The study also found that survivors with greater cognitive deficit had poor educational achievement. The study noted that such deficits were experienced most by survivors who were younger at MD, which possibly explains the impact these would have on educational and vocational achievement as well as social relationships. These impacts would also likely to have been made worse by the fact that many survivors are not followed-up after MD.

It is important that poorer educational achievement in young people post-MD is identified, which in the long-term may affect vocational choices and in turn could lead to loss of financial independence later in life. The absence of support may leave survivors with diminished confidence in their ability to achieve future success.

In terms of practical implications, cognitive deficts may affect aspects of daily life in adolescent survivors. For example, memory and attention problems are likely to affect educational and career progression. Survivors may become very frustrated and tired due to the effort required to focus their attention. This is supported by survivors reporting significantly greater mental fatigue compared to controls. These problems imply that adolescent survivors may benefit from cognitive rehabilitation post MD in order to improve their long-term outcome. Although, compared with paediatric survivors, adolescents showed a relatively milder degree of neuropsychological dysfunction, the clinical relevance of these impairments should not be discounted. Indeed, their presence was associated with clear evidence of educational underachievement.

Many adolescent survivors of MD may function well and appear to live a normal life. However, as the results demonstrate there will be survivors who may continue to experience problems that can affect materially various aspects of their lives. Therefore, community-based paediatricians should routinely follow-up adolescents who have had MD to identify those that require support. Young people post MD in focus groups, as part of a separate study, expressed a strong unmet desire for continued medical review.

From an applied perspective, the results of this study are encouraging in that they suggest potential areas for intervention in order to improve adolescents' quality of life post-MD.

7.2 Future directions

A number of directions for future research that expand upon the work undertaken in this study are discussed below:

Continued investigation of outcomes of MD in survivors is vitally important for determining the nature and scope of their problems in the longer-term and evaluating possible interventions. This study is a critical first step in identifying and understanding outcomes of MD in adolescents. Cross-sectional assessment provides an indication of outcomes but does not provide complete understanding. Therefore, the next logical step is the further longitudinal assessment of outcomes at multiple time points to assess whether the deficits reported here persist beyond the medium-term. Furthermore, combining neuropsychological measurements and functional brain imaging would also enable a more comprehensive assessment and establish the important linkage between neurological insult, the mechanisms and function.

Development of a disease specific QOL measure for young people post MD
Survivors reported a number of areas affected post MD and global reduction in quality of life (QOL). Although this is an important finding, it did not indicate which areas are of significant subjective concern for survivors. Available adolescent QOL instruments judged to be of high quality do not assess the unique impairments that adolescents suffer following MD. The results of the outcome study directed the team towards the development of a screening tool for adolescent MD survivors' in order to identify those who are at increased risk of developing problems and to target the necessary support accordingly. Accurate assessment of subjective as well as objective impacts of MD in adolescence requires the development of a disease-specific QOL instrument that focuses on areas of function relevant to young people post MD, and as a result, most responsive to small but important changes. Deficits, which have the most impact on the life of an individual and the costs to the State of survival from MD, are those that have a subjective as well as objective impact on functioning.

We have recently completed the development of a 39-item measure of QOL for survivors of MD in adolescence and young adulthood (ages 15-26). The measure, called the '*Satisfaction of Life After Meningitis (SLAM)*', is likely to be a valuable tool for clinicians and researchers in assessing QOL in young people.

Further work is also under consideration in the following areas:

Developing interventions for adolescent MD survivors

Findings regarding QOL post MD will be linked to the results of the outcome study to identify areas of significant deficit associated with QOL for young people after MD. As the outcome study and QOL study were undertaken in the same population, this analysis can be done both cross-sectionally and longitudinally within subjects. A sample of young people identified as having objective deficits (as measured on the outcome study) e.g. memory or processing difficulties, functional deficits and/or poor QOL (as measured on the QOL instrument) will be invited to meet with the researcher and investigator (Consultant Clinical Psychologist). This clinical assessment will identify possible interventions that will address those difficulties identified by the young persons as having the greatest impact on their lives. These strategies will be used in conjunction with previous studies of interventions in conditions closely related to MD. This will help define relevant components of interventions and demonstrate the feasibility of delivery as well as acceptability. Different interventions may need to be piloted to achieve optimal effectiveness in both neurorehabilitation and psychological support for survivors of MD. This will inform specific recommendations to health professionals and carers, and provide information for families and young people through support charities.

A physical injuries measure

A questionnaire specific to adolescent survivors of MD will be designed for future research purposes. The questionnaire used in this study was adapted from a physical injuries and disabilities questionnaire developed by the Quebec Occupational Health and Safety Commission for work-related injuries. An age and MD specific questionnaire would be more appropriate for use in future studies.

Rey Auditory Verbal Learning Test

The large quantity of data collected from controls during this test, conducted as part of the outcome study will be published separately, providing the largest set of normative data on this age range.

Item discrimination analyses of mental health measures

As MD was found to increase the risk of depression in survivors, item discrimination analyses (not planned for in this study) on the CORE and Beck Depression Inventory (BDI-II) would provide further insight into individual responses to items between the survivors and controls and thus specific areas causing depression.

In conclusion, the findings of this study are both clinically and scientifically important and have implications for future research directions, after-care delivery and planning of supportive interventions. The findings revealed that medical care for adolescent MD survivors was poor following discharge from hospital suggesting that a high proportion of morbidity in survivors goes unrecognised and therefore untreated. Adolescent survivors of MD have a disturbing series of deficits. MD due to seroGroup B disease remains a major cause of morbidity and mortality in adolescents. Therefore, routine follow-up of adolescent survivors should become standard, in order to prevent or ameliorate physical and psychosocial morbidity after MD and to offer adolescent survivors the support they desire and deserve.

SECTION E

Reference List

Abbott, J. D., Jones, D. M., Painter, M. J., and Young, S. E. J. (1985). The epidemiology of meningococcal infections in England and Wales 1912-83. *J Infect* **11**, 241-257.

Achtman, M. (1995). Global epidemiology of meningococcal disease. In 'Meningococcal disease'. (Ed. J. e. Cartwright.) pp. 159-175. (John Wiley & Sons: Chichester.)

Adams, W. G., Deaver, S. L., Cochi, B. D., Plikaytis, E. R., Zell, C., Broome, V., and Wenger, J. D. (1993). Decline of childhood *Haemophilus influenzae* type b (Hib) disease in the Hib vaccine era. *JAMA* **269**, 221-226.

Advisory Committee on Immunization Practices (1997). Control and prevention of serogroup C meningococcal disease: evaluation and management of suspected outbreaks: recommendations of the Advisory Committee on Immunization Practices. *Morb Mortal Wkly Rep* **46**, 13-21.

Aiken, M. and Gensler, H. (1996). Adjusting for Multiple Testing When Reporting Research Results: The Bonferroni vs Holm Methods. *Am J Public Health* **86**, 726-728.

Almeida-Gonzalez, L., Franco-Paredes, C., Perez, L. F., and Santos-Preciado, J. I. (2004). [Meningococcal disease caused by Neisseria meningitidis: epidemiological, clinical, and preventive perspectives]. *Salud Publica Mex.* **46**, 438-450.

Alter, C. L., Pelcovitz, D., and Axelrod, A. (1996). Identification of PTSD in cancer survivors. *Psychosomatics.* **37**, 137-143.

Altman, D. G. and Bland, J. M. (1995). Absence of evidence is not evidence of absence. *BMJ* **311**, 485.

Andelman, F., Kipervasser, S., Neufield, M. Y., Kramer, U., and Fried, I. (2006). Predictive value of Wada memory scores on postoperative learning and memory abilities in patients with intractable epilepsy. *J Neurosurg* **104**, 20-26.

Anderson, B. M. (1978). Mortality in meningococcal infections. *Scan J Infect Dis* **10**, 277-282.

Anderson, J., Backer, V., and Voldsgaard, P. (1997). Acute meningococcal meningitis: Analysis of features of the disease according to the age of 255 patients. *J Infect* **34**, 227-235.

Anderson, J. and Lind, I. (1994). Characterization of Neisseria meningitidis isolates and clinical features of meningococcal conjunctivitis in ten patients. *Eur.J Clin.Microbiol.Infect.Dis.* **13**, 388-393.

Annett, M. (1985). Left, right, hand and brain: The right shift theory. (Erlbaum: Hillside, NJ.)

Anonymous (1996). Outbreak of meningococcal disease in students in Cardiff. *CDR* **6**, 425.

Anonymous (1997). Clusters of meningococcal disease in university students. *CDR* **7**, 393.

Apicella, M. A. (1995). Neisseria meningitidis. In 'Principles and Practice of Infectious Diseases,'. (G. L. Mandell, J. E. Bennett, and R. Dolin Eds.) pp. 1896-1909. (John Wiley & Sons, Inc: New York.)

Apicella, M. A. (2000). Neisseria Meningitidis. In 'Principles and Practice of Infectious Diseases'. (G. I. Mandel, J. E. Bennett, and R. Dolin Eds.) pp. 2228-2241. (Churchill Livingstone: Philadelphia, PA.)

Araujo, K., Ryst, E., and Steiner, H. (1999). Adolescent Defense Style and Life Stressors. *Child Psychiatry & Human Development* **30**, 19-28.

Ashton, W. A. and Fuehrer, A. (1993). Effects of gender and gender role identification of participant and type of social support resource on support seeking. *Sex Roles.* **28**, 461-476.

Ashwal, S., Stringer, W., Tomasi, L., Schneider, S., Thompson, J., and Perkin, R. (1990). Cerebral blood flow and carbon dioxide reactivity in children with bacterial meningitis. *J Pediatr.* **117**, 523-530.

Auriat, N. (1993). "My wife knows best". A comparison of event dating accuracy between the wife, the husband, the couple, and the Belgium population register. *Public Opinion Quarterly,* **57**, 165-190.

Aycock, W. L. and Mueller, J. H. (1950). Meningococcus carrier rates and meningitis incidence. *Bacteriol Rev* **14**, 115-160.

Baines, P. B. and Hart, C. A. (2003). Severe meningococcal disease in childhood. *Br.J.Anaesth.* **90**, 72-83.

Baker, M., McNicholas, A., Garrett, N., Jones, N., Stewart, J., Koberstein, V., and Lennon, D. (2000). Household crowding a major risk factor for epidemic meningococcal disease in Auckland children. *Pediatr.Infect.Dis.J.* **19**, 983-990.

Ball, J. H. and Young, D. A. (1974). Primary meningococcal pneumonia. *Am Rev.Respir.Dis.* **109**, 480-483.

Baraff, L. J, Lee, S. I, and Schriger, D. L. (1993). Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatr Infect Dis J* **12**, 389-94.

Barkham, M, Gilbert, N., Connell, J., Marshall, C., and Twigg, E. (2005). Suitability and utility of the CORE-OM and CORE-A for assessing severity of presenting problems in psychological therapy services based in primary and secondary care settings. *British Journal of Psychiatry* **186**, 239-246.

Barkham, M, Margison, F, and Leach, C (1998). The rationale for developing and implementing core outcome batteries for routine use in service settings and psychotherapy outcome research. *Journal of Mental Health* **7**, 35-47.

Barkham, M, Margison, F, and Leach, C (2001). Service profiling and outcomes benchmarking using the CORE-OM: toward practice-based evidence in the psychological therapies. *Journal of Consulting & Clinical Psychology* **69**, 184-196.

Baron, P. and Perron, L. M. (1986). Sex Differences in the Beck Depression Inventory Scores of Adolescents. *Journal of Youth and Adolescence* **15**, 165-171.

Barone, C., Iscoe, E., Trickett, E., and Schmid, K. (1998). An Ecologically Differentiated, Multifactor Model of Adolescent Network Orientation. *American Journal of Community Psychology* **26**, 403-423.

Barquet, N., Domingo, P., Cayla, J. A., Gonzalez, J., Rodrigo, C., Fernandez-Viladrich, P., Moraga-Llop, F. A., Marco, F., Vazquez, J., Saez-Nieto, J. A., Casal, J., Canela, J., and Foz, M. (1999). Meningococcal disease in a large urban population (Barcelona, 1987-1992): predictors of dismal prognosis. Barcelona Meningococcal Disease Surveillance Group. *Arch.Intern.Med.* **159**, 2329-2340.

Barquet, N., Gasser, I., Domingo, P., Moraga, F. A., Macaya, A., and Elcuaz, R. (1990). Primary meningococcal conjunctivitis: report of 21 patients and review. *Rev.Infect.Dis.* **12**, 838-847.

Barrera, M. and Garrison-Jones, C. (1992). Family and peer social support as specific correlates of adolescent depressive symptoms. *Journal of Abnormal Child Psychology.* **20**, 1-16.

Bartlett, F. C. (1943). Fatigue following highly skilled work. *Proc R Soc* **B131**, 247-257.

Batty, G. D. and Deary, I. J. (2004). Early life intelligence and adult health. *BMJ* **329**, 585-586.

Beck, A. T. Beck Depression Inventory. 1987. USA, Psychological Corporation.

Beck, A. T., Steer, R. A., and Brown, B. K. (1988). Psychometric properties of Beck Depression Inventory: Twenty five years of evaluation. *Clinical Psychology Review* **8**, 77-100.

Beck, A. T., Steer, R. A., and Brown, G. K. Beck Depression Inventory-Second Edition manual. 1996. San Antonio, TX: The Psychological Corporation.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., and Erbaugh, J. (1961). An inventory for measuring depression. *Arch Gen Psychiatry* **4**, 561-571.

Beck.A.T. (1970). Depression: Causes and Treatment. (University of Pennsylvania Press: Philadelphia, PA.)

Benayoun, R., Guey, J., and Baurand, C. (1969). Etude correlative des donnes cliniques electroencephalographiques et psychologiques chez des traumatises cranio-cerebraux. *Journal de Psychologie Normale et Pathologique* **66**, 167-193.

Bennett, D. S., Ambrosini, P. J., Bianchi, M., Barnett, D., Metz, C., and Rabinovich, H. (1997). Relationship of Beck depression inventory factors to depression among adolescents. *J Affect Disord* **45**, 127-134.

Bennett-Levy, J. (1984a). Determinants of performance on the Rey-Osterrieth Complex Figure Test: An analysis and a new technique for single-case assessment. *British Journal of Clinical Psychology* **23**, 109-119.

Bennett-Levy, J. (1984b). Long-term effects of severe closed head injury on memory: Evidence from a consecutive series of young adults. *Acta Neurol Scand* **70**, 285-298.

Benzer, H., Mutz, N., and Pauser, G. (1983). Psychological sequelae of intensive care. *Intern Anaes Clin* **21**, 169-181.

Berg, E. A. (1948). A simple objective treatment for measuring flexibility in thinking. *Journal of General Psychology* **39**, 15-22.

Berg, I. (1992). Absence from school and mental health. *Br J Psychiatry* **161**, 154-166.

Berg, l. de Marchena O. Focal Infections. In L.P. Rowland (Ed.), Merritt's textbook of Neurology (8th ed.). 1989. Philadelphia, Lea and Febiger.

Berkman, L. F. (1995). The role of social relations in health promotion. *Psychosomatic Medicine* **57**, 245-254.

Berndt, T. J. (1982). The features and effects of friendship in early adolescence. *Child Development.* **53**, 1447-1460.

Berndt, T. J. The morality of friendship versus the morality of individual autonomy: Paper presented at the Biennial Meeting of the International Society for the Study of Behavioural Development. 1996. Quebec, Document reproduction Service ED 400 092.

Berry, D. T. R., Allen, R. S., and Schmitt, F. A. (1991). The Rey-Osterrieth Complex Figure: Psychometric characteristic in geriatric sample. *The Clinical Neuropsychologist* **5**, 143-153.

Bevanger, L., Bergh, K., Gisnas, G., Caugant, D. A., and Froholm, L. O. (1998). Identification of nasopharyngeal carriage of an outbreak strain of Neisseria meningitidis by pulsed-field gel electrophoresis versus phenotypic methods. *J Med Microbiol.* **47**, 993-998.

Biley, F. C. (1994). Effects of noise in hospitals. *Br J Nurs* **3**, 110-112.

Bilukha, O. O. and Rosenstein, N. (2005). Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep* **54**, 1-21.

Bjune, G., Hiby, E. A., Gronnesby, J. K., and Arnesen, O. (1991). Effect of an outer membrane vesicle vaccine against serogroup B meningococcal disease in Norway. *Lancet* **33**, 1093-1096.

Blachstein, V. E. (1997). Rey AVLT: development norms for adults and the sensitivity of different memory measures to age. *Clin Neuropsychol* **11**, 356-369.

Blackwell, C. C., Tzanakaki, G., Kremastinou, J., Weir, P., Vakalis, N., Elton, R. A., Mentis, A., and Fatouros, N. (1992). Factors affecting carriage of Neisseria meningitidis among Greek military recruits. *Epidemiol Infect* **108**, 441-448.

Blackwell, C. C. and Weir, D. M. (1990). Meningococcal disease: high virulence and low transmission. *Lancet* **336**, 53.

Blaser, M. J., Reingold, A. L., Alsever, R. N., and Hightower, A. (1984). Primary meningococcal pericarditis: a disease of adults associated with serogroup C Neisseria meningitidis. *Rev.Infect.Dis.* **6**, 625-632.

Blum, R. W. (1998). Healthy youth development as a model for youth health promotion: A review. *Journal of Adolescent Health* **22**, 368-375.

Boksem, M. A. S., Meijman, T. F., and Lorist, M. M. (2005). Effects of mental fatigue on attention: An ERP study. *Cognitive Brain Research* **25**, 107-116.

Bonferroni, C. E. (1935). Il calcolo delle assicurazioni su gruppi di test. In 'Studi in onore del Professore Salvatore Ortu Carboni'. (Ed. C. E. Bonferroni.) pp. 13-60. Rome, Italy.)

Booy, R, Hodgson, S. A., Slack, M. P., and et al (1993). Invasive *Haemophilus influenzae* type b disease in the Oxford Region (1985-91). *Arch Dis Child* **69**, 225-228.

Booy, R., Habibi, P., Nadel, S., de Munter, C., Britto, J., Morrison, A., and Levin, M. (2001). Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. *Arch.Dis.Child* **85**, 386-390.

Bose, A., Coen, P., Tully, J., Viner, R., and Booy, R. (2003). Effectiveness of meningococcal C conjugate vaccine in teenagers in England. *Lancet* **361**, 675-676.

Boslego, J., Garcia, J., Cruz, C., Zollinger, W., Brandt, B., Ruiz, S., Martinez, M., Arthur, J., Underwood, P., Silva, W. (1995). Efficacy, safety, and immunogenicity of a meningococcal group B (15:P1.3) outer membrane protein vaccine in Iquique, Chile. Chilean National Committee for Meningococcal Disease. *Vaccine* **13**, 821-829.

Boutet, R., Stuart, J. M., Kaczmarski, E. B., Gray, S. J., Jones, D. M., and Andrews, N. (2001). Risk of laboratory-acquired meningococcal disease. *J Hosp.Infect.* **49**, 282-284.

Bradburn, N. M., Rips, L. J., and Shevell, S. K. (1987). Answering Autobiographical Questions: The Impact of Memory and Inference on Surveys. *Science, New Series,* **236**, 157-161.

Bradford-Hill, A. (1965). The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine* **58**, 295-300.

Bradshaw, J. L. (1989). Hemispheric specialization and psychological function. (John Wiley & Sons: Chichester, England.)

Brandtzaeg, P. (2006). Pathogenesis and pathophysiology of invasive meningococcal disease. In 'Handbook of Meningococcal Disease'. (M. Frosch and M. MaidenEds.) pp. 427-480. (Wiley-VGH-Verlag: Weinheim.)

Brandtzaeg, P., Bjerre, A., Ovstebo, R., Brusletto, B., Joo, G. B., and Kierulf, P. (2001). Neisseria meningitidis lipopolysaccharides in human pathology. *J Endotoxin.Res.* **7**, 401-420.

Brandtzaeg, P., Kierulf, P., Gaustad, P., Skulberg, A., Bruun, J. N., Halvorsen, S., and Sorensen, E. (1989a). Plasma endotoxin as a predictor of multiple organ failure and death in systemic meningococcal disease. *J.Infect.Dis.* **159**, 195-204.

Brandtzaeg, P., Mollnes, T. E., and Kierulf, P. (1989b). Complement activation and endotoxin levels in systemic meningococcal disease. *J.Infect.Dis.* **160**, 58-65.

Brandtzaeg, P., Ovsteboo, R., and Kierulf, P. (1992). Compartmentalization of lipopolysaccharide production correlates with clinical presentation in meningococcal disease. *J.Infect.Dis.* **166**, 650-652.

Brazier, J. E., Harper, R., and Jones, N. M. B. (1992). Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* **305**, 160-164.

Breslow, N. E. and Day, N. E. (1983). Statistical Methods in Cancer Research: The Analysis of Case-Control Studies. (IARC Scientific Publications: Lyon.)

Breuner, C. C., Smith, M. S., and Womack, W. M. (2004). Factors Related to School Absenteeism in Adolescents With Recurrent Headache. *Headache: The Journal of Head and Face Pain* **44**, 217.

Brewin, C. R., Andrews, B., and Valentine, J. D. (2000). Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *J Consult Clin Psychol* **68**, 748-766.

Bronner, M. B., Knoester, H., Bos, A. P., Last, B. L., and Grootenhuis, M. (2008). Posttraumatic stress disorder (PTSD) in children after paediatric intensive care treatment compared to children who survived a major fire disaster. *Child and Adolescent Psychiatry and Mental Health* **2**.

Brooker, B, H, Cyr, J, and J. Tables for clinicians to use to convert WAIS-R short forms. J Clin Psychol 42, 983-986. 1986.

Brooks, D. N. (1972). Memory and head injury. *Journal of Nervous and Mental Disease* **155**, 350-355.

Brooks, R., Kerridge, R., Hillman, K., Bauman, A., and Daffurn, K. (1997). Quality of life outcomes after intensive care: Comparison with a community group. *Intensive Care Med* **23**, 581-586.

Brooks, W. M., Stidley, C. A., Weers, D. C., Friedman, S. D., Barlow, M. A., Wilmer, L., Sibbitt, R., and Yeo, A. (2000). Metabolic and Cognitive Response to Human Traumatic Brain Injury: A Quantitative Proton Magnetic Resonance Study. *Journal of Neurotrauma* **17**, 629-640.

Broomhead, R. L. and Brett, S. J. (2002). Clinical review: Intensive care follow-up - what has it told us? *Critical Care*.

Brown, A. S. (2000). Neurocognitive functioning of adolescents: effects of protracted alcohol use. *Alcohol Clin Exp Res* **24**, 164-171.

Brown, G. and Harris, T. (1978). Social Origins of Depression. (Tavistock Press: London.)

Brown, I. D. (1994). Driver fatigue. *Hum Factors* **36**, 298-314.

Bruce, M. G., Rosenstein, N. E., Capparella, J. M., Shutt, K. A., Perkins, B. A., and Collins, M. (2001). Risk factors for meningococcal disease in college students. *JAMA* **286**, 688-693.

Bruns, H. and Hohn, J. (1908). Über den Nachweis und das Vorkommen der Meningocokokken im Nasenrachenraum. *Klin. Jahrb.* **18**, 825.

Buchwald, D. S., Rea, W. J., and Katon et al. (2000). Acute infectious mononucleosis: Characteristics of patients who report failure to recover. *Am J Med* **109**, 531-537.

Butler, S., Chalder, T., Ron, M., and Wessely, S. (1991). Cognitive behaviour therapy in chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry* **54**, 153-158.

Bygraves, J. A., Urwin, R., Fox, A. J., Gray, S. J., Russell, J. E., Feavers, I. M., and Maiden, M. C. (1999). Population genetic and evolutionary approaches to analysis of Neisseria meningitidis isolates belonging to the ET-5 complex. *J.Bacteriol.* **181**, 5551-5556.

Byrd, R. S. (2005). School Failure: Assessment, Intervention, and Prevention in Primary Pediatric Care. *Pediatrics in Review* **26**, 233-243.

Call, K. T. and Mortimer, J. T. (2001). Areas of comfort in adolescence: A study of adjustment in context. (Lawrence Erlbaum Associates: Mahwah NJ.)

Capuron, L., Welberg, L., Heim, C., Wagner, D., Solomon, L., Papanicolaou, D. A., Craddock, R. C., Miller, A. H., and Reeves, W. C. (2006). Cognitive dysfunction relates to subjective report of mental fatigue in patients with chronic fatigue syndrome. *Neuropsychopharmacology* **31**, 1777-1784.

Carrol, E. D., Thomson, A. P., Shears, P., Gray, S. J., Kaczmarski, E. B., and Hart, C. A. (2000). Performance characteristics of the polymerase chain reaction assay to confirm clinical meningococcal disease. *Arch.Dis.Child* **83**, 271-273.

Carter, B. D., Edwards, J. F., and Kronenberger et al. (1995). Case control study of chronic fatigue in pediatric patients. *Pediatrics* **95**, 179-186.

Cartwright, K. (1995a). Introduction and historical aspects. In 'Meningococcal Disease'. pp. 1-9.

Cartwright, K. (1995b). Meningococcal carriage and disease: Meningococcal Disease. (John Wiley & Sons: London.)

Cartwright, K. and Kroll, S. (1997). Optimising the investigation of meningococcal disease. *BMJ* **315**, 757-758.

Cartwright, K., Strang, J., Gossain, S., and Begg, N. (1992). Early treatment of meningococcal disease. *BMJ* **305**, 774.

Cartwright, K., Stuart, J. M., Jones, D. M., and Noah, N. D. (1987). The Stonehouse survey:nasopharyngeal carriage of meningococci and Neisseria lactamica. *Epidemiol Infect* **99**, 591-601.

Cartwright, K. A. (1999). Early management of meningococcal disease. *Infect.Dis.Clin.North Am.* **13**, 661-84, viii.

Cartwright, K. A., Jones, D. M., Smith, A. J., Stuart, J. M., Kaczmarski, E. B., and Palmer, S. R. (1991a). Influenza A and meningococcal disease. *Lancet* **338**, 554-557.

Cartwright, K. A., Stuart, J. M., and Robinson, P. M. (1991b). Meningococcal carriage in close contacts of cases. *Epidemiol.Infect.* **106**, 133-141.

Carty, L. (1989). Social support, peer counselling and the community counsellor. *Canadian Journal of Counselling* **23**, 92-102.

Cassens, G., Wolfe, L., and Zola, M. (1990). The neuropsychology of depressions. *Journal of Neuropsychiatry and Clinical Neurosciences* **2**, 202-213.

Cauce, A. M., Mason, C., Gonzales, N., Hiraga, Y., and Liu, G. (1996). Social support during adolescence: Methodological and theoretical considerations. In 'Social problems and social context in adolescence: perspectives across boundaries.'. pp. 131-151. (Aldine de Gruyter.: Hawthorne, New York.)

Caugant, D. A. (1998). Population genetics and molecular epidemiology of Neisseria meningitidis. *APMIS* **106**, 505-525.

Caugant, D. A., Hoiby, E. A., Magnus, P., Scheel, O., Hoel, T., Bjune, G., Wedege, E., Eng, J., and Froholm, L. O. (1994). Asymptomatic carriage of Neisseria meningitidis in a randomly sampled population. *J Clin.Microbiol.* **32**, 323-330.

Cavill, S. and Bryden, P. (2003). Development of handedness: Comparison of questionnaire and performance-based measures of preference. *Brain and Cognition* **53**, 149-151.

Ceesay, S. J., Allen, S. J., Menon, A., Todd, J. E., Cham, K., Carlone, G. M., Turner, S. H., Gheesling, L. L., DeWitt, W., Plikaytis, B. D., and . (1993). Decline in meningococcal antibody levels in African children 5 years after vaccination and the lack of an effect of booster immunization. *J.Infect.Dis.* **167**, 1212-1216.

Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., and Wallace, E. P. (1993). Development of a fatigue scale. *J Psychosom Res* **37**, 147-153.

Chari, G., Shaw, P. J., and Sahgal, A. (1996). Nonverbal visual attention, but not recognition memory or learning, processes are impaired in motor neurone disease. *Neuropsychologia* **34**, 377-385.

Cher, D. J., Maxwell, W. J., Frusztajer, N., Marin, M., and Wiviott, L. D. (1993). A case of pelvic inflammatory disease associated with Neisseria meningitidis bacteremia. *Clin.Infect.Dis.* **17**, 134-135.

Christie, D., Leiper, A. D., Chessells, J. M., and Vargha-Khadem, F. (1995). Intellectual performance after pre-symptomatic cranial radiotherapy for leukaemia: effects of age and sex. *Arch Dis Child* **73**, 136-140.

Cleary, P. D. (2003). A hospitalization from hell: a patient's perspective on quality. *Ann.Intern.Med* **138**, 33-39.

Coen, P. G., Cartwright, K., and Stuart, J. (2000). Mathematical modelling of infection and disease due to Neisseria meningitidis and Neisseria lactamica. *Int. J. Epidemiol.* **29**, 180-188.

Coen, P. G., Tully, J., Stuart, J. M., Ashby, D., Viner, R. M., and Booy, R. (2006). Is it exposure to cigarette smoke or to smokers which increases the risk of meningococcal disease in teenagers? *International Journal of Epidemiology* **35**, 330-336.

Cohen, P., Cohen, J., and Brook, J. (1993). An epidemiological study of disorders in late childhood and adolescence. II. Persistence of disorders. *Journal of Child Psychology and Psychiatry* **34**, 869-877.

Cohen, S. (1992). Stress, social support and disorder. In 'The Meaning and Measurement of Social Support'. (H. O. Veiel and U. Baumann Eds.) pp. 109-124. (Hemisphere Publishing: New York.)

Colarossi, L. G. and Eccles, J. S. (2000). A Prospective Study of Adolescents' Peer Support: Gender Differences and the Influence of Parental Relationships. *Journal of Youth and Adolescence* **29**, 661-678.

Colditz, G. A., Brewer, T. F., and Berkey, C. S. (1994). Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA* **271**, 698-702.

Coleman, C., Friedman, A., and Burright, R. G. (1998). The relationship of daily stress and health-related behaviors to adolescents' cholesterol levels. *Adolescence* **33**, 447-460.

Commission de la Santé et de la Sécurité du Travail. Règlement annoté sur le barème des dommages corporels [in French]. 1987. Montreal.
Ref Type: Report

Conner, W. T. and Minielly, J. A. (1980). Cerebral oedema in fatal meningococcaemia. *Lancet* **2**, 967-969.

Connolly, M. and Noah, N. (1999). Is group C meningococcal disease increasing in Europe? A report of surveillance of meningococcal infection in Europe 1993-6. *Epidemiol Infect* **122**, 41-49.

Conyn-van Spaendonck, M. A., Reintjes, R., Spanjaard, L., van Kregten, E., Kraaijeveld, A. G., and Jacobs, P. H. (1999). Meningococcal carriage in relation to an outbreak of invasive disease due to Neisseria meningitidis serogroup C in the Netherlands. *J.Infect.* **39**, 42-48.

Core System Group. CORE System (Information Management) Handbook. -Leeds. 1998. Core System Group.

Coull, J. T., Frith, C. D., Frackowiak, R. S. J., and Grasby, P. M. (1996). A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. *Neuropsychologia* **34**, 1085-1095.

Covington, M. V. (1989). Self-esteem and Failure in School. The Social Importance of Self-Esteem. (University of Cambridge Press: Berkeley, CA.)

Cox, D. R. and Wermuth, N. (2001). Causal inference and statistical fallacies. In 'International Encyclopedia of the Social and Behavioral Sciences'. (P. B. Baltes and N. J. Smelser Eds.) pp. 1554-1661. (Elsevier: Amsterdam.)

Crawford, J. R. (1989). Estimation of premorbid intelligence: A review of recent developments. In 'Developments in clinical and experimental neuropsychology'. (J. R. Crawford and D. M. Parker Eds.) pp. 55-74. (Plenum Press: New York.)

Crawford, J. R. (1992). Current and premorbid intelligence measures in neuropsychological assessment. In 'Handbook of Neuropsychological assessment'. (J. R. Crawford, D. M. Parker, and W. M. MacKinlay Eds.) pp. 21-49. (Taylor and Francis: London.)

Crawford, J. R., Parker, D. M., and Besson, J. A. (1988). Estimation of premorbid intelligence in organic conditions . *The British Journal of Psychiatry* **153**, 178-181.

Crofton, J. and Douglas, A. (1981). Respiratory Diseases. (Oxford: Blackwell Scientific Publications:

Crovitz, H. F. and Zener, K. A. (1962). A group test for assessing hand and eye dominance. *Am J Psychol.* **47**, 191-196.

Cuthbertson, B. H., Hull, A., Strachan, M., and Scott, J. (2004). Post-traumatic stress disorder after critical illness requiring general intensive care. *Intensive Care Med* **30**, 450-455.

Damos, D. L. and Parker, E. S. (1994). High false alarm rates on a vigilance task may indicate recreational drug use. *Journal of Clinical and Experimental Neuropsychology* **16**, 713-722.

Danielson, L. and Mann, E. (1806). The history of a singular and very mortal disease, which lately made its appearance in Medfield. *Med Agric Reg* **1**, 65.

Danzig, L. (2004). Meningococcal vaccines. *Pediatr.Infect.Dis.J* **23**, S285-S292.

Dashefsky, B., Teele, D. W., and Klein, J. O. (1983). Unsuspected meningococcemia. *J Pediatr.* **102**, 69-72.

Davison, K. L., Ramsay, M. E., Crowcroft, N. S., Lieftucht, A., Kaczmarski, E. B., Trotter, C. L., Gungabissoon, U., and Begg, N. T. (2002). Estimating the burden of serogroup C meningococcal disease in England and Wales. *Commun.Dis.Public Health* **5**, 213-219.

Dawson, J. A. and Wardle, R. (1990). Detection and prevalence of hearing loss in a cohort of children following serogroup B, meningococcal infection 1983-1987. *Public Health* **104**, 99-102.

de Gans, J. and van de Beek, D. (2002). Dexamethasone in adults with bacterial meningitis. *N.Engl.J.Med* **347**, 1549-1556.

De Luca, C. R., Wood, S. J., Anderson, V., Buchanan, J. A., Proffitt, T. M., and Mahoney, K. (2003). Normative data from the CANTAB. I: development of executive function over the lifespan. *Journal of Clinical and Experimental Neuropsychology* **25**, 242-254.

De Moraes, J. C., Perkins, B. A., Camargo, M. C., Hidalgo, N. T., Barbosa, H. A., Sacchi, C. T., Landgraf, I. M., Gattas, V. L., Vasconcelos, Hde G., (1992). Protective efficacy of a serogroup B meningococcal vaccine in Sao Paulo, Brazil. *Lancet* **340**, 1074-1078.

De Vries, J., Michielsen, H. J., and Van Heck, G. L. (2003). Assessment of fatigue among working people: a comparison of six questionnaires. *Occup Environ Med* **60**, 10-15.

De Wals, P. (2006). Immunization strategies for the control of serogroup C meningococcal disease in developed countries. *Expert. Rev Vaccines.* **5**, 269-275.

De Wals, P., Hertoghe, L., Borlee-Grimee, I., Maeyer-Cleempoel, S., Reginster-Haneuse, G., Dachy, A., Bouckaert, A., and Lechat, M. F. (1981). Meningococcal disease in Belgium. Secondary attack rate among household, day-care nursery and pre-elementary school contacts. *J.Infect.* **3**, 53-61.

Deal, W. B. and Sanders, E. (1969). Efficacy of rifampin in treatment of meningococcal carriers. *N Engl.J Med* **281**, 641-645.

Deale, A., Chalder, T., and Marks, I. (1997). Cognitive behaviour therapy for chronic fatigue syndrome: a randomized controlled trial. *Am J Psychiatry* **154**, 408-414.

Deary, I. J., Whiteman, M. C., Starr, J. M., Whalley, L. J., and Fox, H. C. (2004). The impact of childhood intelligence on later life: following up the Scottish mental surveys of 1932 and 1947. *J Pers.Soc.Psychol* **86**, 130-147.

Delaney, R. C., Prevey, M. L., Cramer, L., and Mattson, R. H. (1988). Test-retest comparability and control subject data for the PASAT, Rey-AVLT, and Rey-Osterrieth/Taylor figures. *Journal of Clinical and Experimental Neuropsychology* **10**, 44 (abstract).

Demeray, M. K. and Malecki, C. K. (2002). The relationship between perceived social support and maladjustment for students at risk. *Psychology in the Schools.* **39**, 305-316.

Department of Health. Immunisation against infectious diseases. Replacement chapter 25: Pneumococcal. 2004a. Crown.

Department of Health, Department for Education and Skills. UK National Service Framework for Children and Young People. 2004b. Crown.

DeWals, P., Hertoghe, L., Borlée-Grimée, I., and et al (1981). Meningococcal disease in Belgium. Secondary attack rate among household, day-care nursery and pre-elementary school contacts. *J* **3**, 53-61.

Djupesland, G. and Gedde-Dahl, T. W. (1983). Sequelae of meningococcal disease - studied about six weeks after hospital admission. *NIPH Ann* **6**, 85-90.

DOH. Reference Costs. www.doh.gov.uk/nhsexec/refcosts.htm . 2004.

Dolan, M. and Park, I. (2002). The neuropsychology of antisocial personality disorder. *Psychological Medicine* **32**, 417-427.

Dominguez, A., Cardenosa, N., Izquierdo, C., Sanchez, F., Margall, N., Vazquez, J. A., and Salleras, L. (2001). Prevalence of Neisseria meningitidis carriers in the school population of Catalonia, Spain. *Epidemiol.Infect.* **127**, 425-433.

Dorion, A. A., Sarazin, M., Hasbourn, D., Hahn-Barma, V., Dubois, B., and Zouaoui, A. (2002). Relationship between attentional performance and corpus callosum morphometry in patients with Alzheimer's disease. *Neuropsychologia* **40**, 946-956.

Downes, J. J., Roberts, A. C., Sahakian, B. J., Evenden, J. L., Heald, A., Morris, R. G., and Robbins, T. W. (1989). Impaired extra dimensional set-shifting performance in medicated and unmedicated Parkinson's disease: Evidence for a specific attentional dysfunction. *Neuropsychologia* **27**, 1329-1343.

Dozois, D. J., Dobson, K. S., and Ahnberg, J. L. (1998). A psychometric evaluation of the Beck Depression Inventory-II. *Psychological Assessment* **10**, 83-89.

Drake, R., Dravitski, J., and Voss, L. (2000). Hearing in children after meningococcal meningitis. *Journal of Paediatrics and Child Health* **36**, 240-243.

Eagger, S. A., Levy, R., and Sahakian, B. J. (1991). Tacrine in Alzheimer's disease. *The Lancet* **337**, 989-992.

Eddleston, J. M., White, P., and Guthrie, E. (2000). Survival, morbidity, and quality of life after discharge from intensive care. *Crit Care Med* **28**, 2293-2299.

Edwards, A. L. (1953). The relationship between the judged desirability of a trait and the probability that it will be endorsed. *Journal of Applied Psychology* **37**, 90-93.

Edwards, E. A., Devine, L. F., Sengbusch, G. H., and Ward, H. W. (1977). Immunological investigations of meningococcal disease. III. Brevity of group C acquisition prior to disease occurrence. *Scand.J Infect.Dis.* **9**, 105-110.

Edwards, M. S. and Baker, C. J. (1981). Complications and sequelae of meningococcal infections in children. *The Journal of Pediatrics* **99**, 540-545.

Elliott, R., McKenna, P. J., Robbins, T. W., and Sahakian, B. J. (1995). Neuropsychological evidence for fronto-striatal dysfunction in schizophrenia. *Psychological Medicine* **25**, 619-630.

Elliott, R., Sahakian, B. J., McKay, A. P., Herrod, J. J., Robbins, T. W., and Paykel, E. S. (1996). Neuropsychological impairments in unipolar depression: the influence of perceived failure on subsequent performance. *Psychological Medicine* **26**, 975-989.

Ellison, R. T. III, Kohler, P. F., Curd, J. G., Judson, F. N., and Reller, L. B. (1983). Prevalence of congenital or acquired complement deficiency in patients with sporadic meningococcal disease. *N Engl J Med* **30**, 913-916.

English, K. M. (2002). Counseling children with hearing impairment and their families. (Allyn and Bacon.: Boston.)

Erickson, E. H. (1959). Identity and the life-cycle. *Psychol Issues* **1**, 164.

Erickson, L. and De Wals, P. (1998). Complications and sequelae of meningococcal disease in Quebec, Canada, 1990-1994. *Clin.Infect.Dis.* **26**, 1159-1164.

Erickson, L. J., De Wals, P., McMahon, J., and Heim, S. (2001). Complications of meningococcal disease in college students. *Clin.Infect.Dis.* **33**, 737-739.

Ermisch, J. and Francesconi, M. The Effect of Parents' Employment on Children's Lives. 2001. London, Family Policy Study Centre for the Joseph Foundation.

EU-IBIS Network. Invasive Neisseria Meningitidis in Europe 2003/2004. 2006. London, Health Protection Agency.

EU-MenNet. Impact of meningococcal epidemiology and population biology on public health in Europe, Final report 2001-2005. 2007.

European Centre for Disease Prevention and Control. The First European Communicable Disease Epidemiological Report. Amato-Gauci, A. and Ammon, A. 2007. http://www.ecdc.eu.int/pdf/Epi_report_2007.pdf.

EuroQol Group. (1990). EuroQol-A new facility for the measurement of health-related quality of life. *Health Policy.* **16**, 199-208.

Evans, A. S. and Niederman, J. C. (1998). Epstein-Barr Virus. In 'Viral infections of humans: epidemiology and control'. (A. S. Evans and R. A. KaslowEds.) pp. 253-280. (Plenum Press: New York.)

Evans, C, Connell, J, and Barkham, M (2002). Towards a standardised brief outcome measure psychometric properties and utility of the CORE-OM. *British Journal of Psychiatry* **180**, 51-60.

Fallon, R. J., Brown, W. M., and Lore, W. (1984). Meningococcal infection in Scotland 1972-82. *J Hyg* **3**, 167-180.

Farrell, D. G. and Dahl, E. V. (1966). Nasopharyngeal carriers of N. meningitidis: Studies among Air Force recruits. *JAMA* 1189-1192.

Feder, H. M., Dworkin, P. H., and Orkin, C. (1994). Outcome of 48 pediatric patients with chronic fatigue. A clinical experience. *Arch Fam Med* **3**, 1049-1055.

Feigin, R. D., Stechenberg, B. W., Change, M. J., and et al (1976). Prospective evaluation of treatment of Haemophilus influenzae meningitis. *J Pediatr* **88**, 542-548.

Feigin, R. D. McCraken Jr G. H. and Klein J. O. Diagnosis and management of meningitis. Pediatric Infectious Disease Journal 11, 785-814. 1992.

Feldman, H. M. and Michaels, R. H. (1988). Academic achievement in children ten to 12 years after Haemophilus influenzae meningitis. *Pediatrics* **1**, 339-344.

Fellick, J. M., Sills, J. A., Marzouk, O., Hart, C. A., Cooke, R. W., and Thomson, A. P. (2001). Neurodevelopmental outcome in meningococcal disease: a case-control study. *Arch.Dis.Child* **85**, 6-11.

Fergusson, D. M. and Woodward, L. J. (2002). Mental Health, Educational, and Social Role Outcomes of Adolescents With Depression . *Arch Gen Psychiatry* **59**, 225-231.

Figueroa, J. E. and Densen, P. (1991). Infectious diseases associated with complement deficiencies. *Clin.Microbiol.Rev.* **4**, 359-395.

Finne, J., Leinonen, M., and Makela, P. H. (1983). Antigenic similarities between brain components and bacteria causing meningitis. Implications for vaccine development and pathogenesis. *Lancet* **2**, 355-357.

Fischer, M., Hedberg, K., Cardosi, P., Plikaytis, B. D., Hoesly, F. C., Steingart, K. R., Bell, T. A., Fleming, D. W., Wenger, J. D., and Perkins, B. A. (1997). Tobacco smoke as a risk factor for meningococcal disease. *Pediatr.Infect.Dis.J* **16**, 979-983.

Fisher, R. A. (1950). Statistical methods for research workers. (Oliver and Boyd: London.)

Flaatten, H. and Kvale, R. (2001). Survival and quality of life 12 years after ICU. A comparison with the general Norwegian population. *Intensive Care Med* **27**, 1005-1011.

Flexner, S. (1913). The results of serum treatment in thirteen hundred cases of epidemic meningitis. *J Exp Med* **17**, 553-576.

Flick, S. N. (1988). Managing attrition in clinical research. *Clinical Psychology Review* **8**, 499-515.

Fontanals, D., Van Esso, D., Pons, I., Pineda, V., Sanfeliu, I., Mariscal, D., and Vazquez, J. A. (1995). [Prevalence of Neisseria meningitidis carriers among the population of Cerdanyola (Barcelona)]. *Enferm.Infecc.Microbiol.Clin.* **13**, 398-405.

Foster, M. T., Sanders, E., and Ginter, M. (1971). Epidemiology of sulphonamide resistant meningococcal infections in a civilian population. *American Journal of Epidemiology* **3**, 346-353.

Franke, E. L. and Neu, H. C. (1981). Postsplenectomy infection. *Sur Clin N Am* **61**, 135-155.

Fray, P. J., Robbins, T. W., and Sahakian, B. J. (1997). Neuropsychiatric applications of CANTAB. *International Journal of Geriatric Psychiatry* **11**, 329-336.

Frieling, J. T., van Deuren, M., Wijdenes, J., van Dalen, R., Bartelink, A. K., van der Linden, C. J., and Sauerwein, R. W. (1996). Interleukin-6 and its soluble receptor during acute meningococcal infections: effect of plasma or whole blood exchange. *Crit Care Med* **24**, 1801-1805.

Galimand, M., Gerbaud, G., Guibourdenche, M., Riou, J. Y., and Courvalin, P. (1998). High level chloramphenicol resistance in *Neisseria meningitidis*. *N Engl.J Med* **339**, 868-874.

Garbarino, S. J. and Schellenbach, C. (1984). Families at risk for destructive parent-child relations in adolescence. *Child Dev* **55**, 174-183.

Garnefski, N. and Diekstra, R. (1996). Perceived Social Support from Family, School, and Peers: Relationship with Emotional and Behavioral Problems among Adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry.* **35**, 1657-1664.

Garton, A. F. and Pratt, C. (1987). Participation and interest in leisure activities by adolescent school children. *Journal of Adolescence* **10**, 341-351.

Gaunt, P. N. and Lambert, B. E. (1988). Single dose ciprofloxacin for the eradication of pharyngeal carriage of Neisseria meningitidis. *J Antimicrob. Chemother.* **21**, 489-496.

Geckova, A., van Dijk, J. P., Stewart, R., Groothoff, J. W., and Post, D. (2003). Influence of social support on health among gender and socio-economic groups of adolescents. *European Journal of Public Health.* **13**, 44-50.

Gedde-Dahl, T. W., Hoiby, E. A., and Eskerud, J. R. (1990). Unbiased evidence on early treatment of suspected meningococcal disease. *Rev.Infect.Dis.* **12**, 359, 361-359, 364.

Gelb, L. D. (1990). Infections: bacteria, fungi, and parasites. In 'Neurobiology of disease'. (A. L. Pearlman and R. C. Collins Eds.) (Oxford University Press: New York.)

Gelfand, M. S., Cleveland, K. O., Campagna, C., and Zolyomi, A. (1998). Meningococcal cellulitis and sialadenitis. *South. Med J* **91**, 287-288.

George, A. C. and Melegara, A. (2003). Invasive pneumococcal infection, England and Wales 2003. *CDR Weekly: 2003* 3-9.

Ghandour, R. M., Overpeck, M. D., Huang, Z. J., Kogan, M. D., and Scheidt, P. C. (2004). Headache, stomachache, backache, and morning fatigue among adolescent girls in the United States: associations with behavioral, sociodemographic, and environmental factors. *Arch Pediatr Adolesc Med* **158**, 797-803.

Giedd, J. N. (2004). Structural magnetic resonance imaging of the adolescent brain. *Ann N Y Acad Sci* **1021**, 77-85.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., Paus, T., Evans, A. C., and Rapoport, J. L. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci* **2**, 861-863.

Giedd, J. N., Vaituzis, A. C., Hamburger, S. D., Lanage, N., Rajapakse, J. C., Kaysen, D., Vauss, Y. C., and Rapoport, J. L. (1996). Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development: ages 4-18 years. *Journal of Comparative Neurology* **366**, 23-230.

Gilmore, A., Jones, G., Barker, M., Soltanpoor, N., and Stuart, J. M. (1999). Meningococcal disease at the University of Southampton: outbreak investigation. *Epidemiol.Infect.* **123**, 185-192.

Girard, M. P., Preziozi, M. T., Aguado, M. T., and Kieny, M. P. (2006). A review of vaccine research and development: meningococcal disease. *Vaccine* **24**, 4692-4700.

Glatt, S. L., Hubble, J. P., and Lyons, K. (1996). Risk factors for dementia in Parkinson's disease: effect of education. *Neuroepidemiology* **15**, 20-25.

Gold, R., Goldschneider, I., Lepow, M. L., Draper, T. F., and Randolph, M. (1978). Carriage of Neisseria meningitidis and Neisseria lactamica in infants and children. *J Infect.Dis.* **137**, 112-121.

Goldacre, M. J., Roberts, S. E., and Yeates, D. (2003). Case fatality rates for meningococcal disease in an English population, 1963-98: database study. *BMJ* **327**, 596-597.

Goldschneider, I., Gotschlich, E. C., and Artenstein, M. S. (1969). Human immunity to the meningococcus. I. The role of humoral antibodies. *J Exp.Med* **129**, 1307-1326.

Gooding, D. C., Kwapil, T. R., and Tallent, K. A. (1999). Wisconsin Card Sorting Test deficits in schizotypic individuals. *Schizophrenia Research* **40**, 201-209.

Gossain, S., Constantine, C. E., and Webberley, J. M. (1992). Early parenteral penicillin in meningococcal disease. *BMJ* **305**, 523-524.

Grant, M. M., Thase, M. E., and Sweeney, J. A. (2001). Cognitive disturbance in outpatient depressed younger adults: Evidence of modest impairment. *Biological Psychiatry* **50**, 35-43.

Green, D. M. and Swets, J. A. (1966). Signal Detection Theory and Psychophysics. (Wiley: New York.)

Greenberg, M. (2006). Promoting Resilience in Children and Youth: Preventive Interventions and Their Interface with Neuroscience. *Annals New York Academy of Sciences* **1094**, 139-150.

Greene, T. (2000). Are Observational Studies' Just as Effective as Randomized Clinical Trials? *Blood Purif* **18**, 317-322.

Greenhalgh, T. (1997). Assessing the methodological quality of published papers. *BMJ* **315**, 305-308.

Greenwood, B. M., Bradley, A. K., and Wall, R. A. (1985). Meningococcal disease and season in sub-Saharan Africa
1. *Lancet* **2**, 829-830.

Griffiss, J. M., Yamasaki, R., Estabrook, M., and Kim, J. J. (1991). Meningococcal molecular mimicry and the search for an ideal vaccine. *Trans.R.Soc.Trop.Med Hyg.* **85 Suppl 1**, 32-36.

Grimes, D. and Schulz, K (2002a). Bias and causal association in observational research. *Lancet* **359**, 248-252.

Grimes, D. A. and Schulz, K. F. (2002b). Cohort studies: marching towards outcome. *Lancet* **359**, 341-345.

Grimwood, K., Anderson, P., Anderson, V., Tan, L., and Nolan, T. (2000). Twelve year outcomes following bacterial meningitis: further evidence for persisting effects. *Arch Dis Child* **3**, 111-116.

Grimwood, K., Anderson, V., Bond, L., and et al (1995). Adverse outcomes of bacterial meningitis in school-age survivors. *Pediatrics* **5**, 646-656.

Grimwood, K., Nolan, T., Bond, L., Anderson, V. A., Catroppa, C., and Keir, E. (1996). Risk factors for adverse outcomes of bacterial meningitis. *J Pediatr Child Health* **32**, 457-462.

Gronwell, D. and Wrightson, P. (1981). Memory and information processing capacity after closed head injury. *Journal of Neurology, Neurosurgery, and Psychiatry.* **44**, 889-895.

Hackett, S. J., Guiver, M., Marsh, J., Sills, J. A., Thomson, A. P., Kaczmarski, E. B., and Hart, C. A. (2002). Meningococcal bacterial DNA load at presentation correlates with disease severity. *Arch.Dis.Child* **86**, 44-46.

Hahne, S. J., Charlett, A., Purcell, B., Samuelsson, S., Camaroni, I., Ehrhard, I., Heuberger, S., Santamaria, M., and Stuart, J. M. (2006). Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: systematic review. *BMJ* **332**, 1299-1303.

Hahne, S. J., Gray, S. J., Jean, Francois, Aguilera, Crowcroft, N. S., Nichols, T., Kaczmarski, E. B., and Ramsay, M. E. (2002). W135 meningococcal disease in England and Wales associated with Hajj 2000 and 2001. *Lancet* **359**, 582-583.

Halstensen, A., Pedersen, S. H., Haneberg, B., Bjorvatn, B., and Solberg, C. O. (1987). Case fatality of meningococcal disease in western Norway. *Scand.J.Infect.Dis.* **19**, 35-42.

Haneberg, B., Tonjum, T., Rodahl, K., and Gedde-Dahl, T. (1983). Factors preceding the onset of meningococcal disease with special emphasis on passive smoking, stressful events, physical fitness, and general symptoms of ill health. *NIPH Annals* **6**, 169-174.

Harnden, A., Ninis, N., Thompson, M., Perera, R., Levin, M., Mant, D., and Mayon-White, R. (2006). Parenteral penicillin for children with meningococcal disease before hospital admission: case-control study. *BMJ* **332**, 1295-1298.

Harris, A. D., Bradham, D. D., Baumgarten, M., Zuckerman, I. H., Fink, J. C., and Perencevich, E. N. (2004). The Use and Interpretation of Quasi-Experimental Studies in Infectious Diseases. *Clinical Infectious Diseases* **38**, 1586-1591.

Harris, J. G., Adler, L. E., Young, D. A., Munroe Cullum, C., Rilling, L. M., Cicerello, A., Intemann, P. M., and Freedman, R. (1996). Neuropsychological dysfunction in parents of schizophrenics. *Schizophrenia Research* **20**, 253-260.

Harrison, L. H. (2006). Prospects for Vaccine Prevention of Meningococcal Infection. *Clinical Microbiology Reviews* **19**, 142-164.

Harrison, L. H., Armstrong, C. W., Jenkins, S. R., Harmon, M. W., Ajello, G. W., Miller, G. B., Jr., and Broome, C. V. (1991). A cluster of meningococcal disease on a school bus following epidemic influenza. *Arch.Intern.Med* **151**, 1005-1009.

Harrison, L. H. and Broome, C. V. (1987). The epidemiology of meningococcal meningitis in the U.S. civilian population. In 'Evolution of meningococcal disease'. (Ed. N. Vedros.) pp. 27-45. (CRC Press: Boca Raton, Fla.)

Harrison, L. H., Pass, M. A., Mendelsohn, A. B., Egri, M., Rosenstein, N. E., Bustamante, A., Razeq, J., and Roche, J. C. (2001). Invasive meningococcal disease in adolescents and young adults. *JAMA* **286**, 694-699.

Harter, S. (1986). Processes underlying the construction, maintenance, and enhancement of the self-concept in children. *Psychology perspectives on the self* **3**, 136-182.

Hastings, L., Stuart, J., Andrews, N., and Begg, N. (1997). A retrospective survey of clusters of meningococcal disease in England and Wales, 1993 to 1995: estimated risks of further cases in household and educational settings. *Commun.Dis.Rep.CDR Rev.* **7**, R195-R200.

Health Protection Agency. Invasive meningococcal infections, England and Wales, 2003 and 2004. 2007a.

Health Protection Agency. Statutory Notifications of Infectious Diseases in England & Wales: Provisional Midi Report for 2006. 2007b.

Health Protection Agency Meningococcus Forum. Guidance for public health management of meningococcal disease in the UK. 2006.

Heckels, J. E. (1989). Structure and function of pili of pathogenic Neisseria species. *Clin Microbiol Rev* **2 Suppl**, S66-S73.

Henderson, S., Byrne, D. G., and Duncan-Jones, O. (1981). Neurosis and the Social Environment. (Academic Press: New York.)

Hendry, L. B. (1983). Up and Going Out: Adolescents and leisure. (Aberdeen University Press.: Aberdeen.)

Hennekens, C. H. and Buring, J. E. (1987). Epidemiology in Medicine. (Lippincott Williams & Wilkins: Philadelphia, PA.)

Hernan, M. A. and Robins, J. M. (2006). Instruments for Causal Inference *An Epidemiologist's Dream? Epidemiology* **17**, 360-372.

Herrick, W. W. (1919). Extramengeal meningococcus infections. *Arch Intern Med* **23**, 409-418.

Hibberd, M. L., Sumiya, M., Summerfield, J. A., Booy, R., and Levin, M. (1999). Association of variants of the gene for mannose-binding lectin with susceptibility to meningococcal disease. Meningococcal Research Group. *Lancet* **353**, 1049-1053.

Hirsch, A. (1886). Epidemic cerebro-spinal meningitis. In 'Handbook of geographical and historical pathology (translated from the German by Creighton C.)'. pp. 547-594. (New Sydenham Society.: London.)

HMSO. The Public Health (Infectious Diseases) Regulations 1988. 1988

Hoare, S. (1999). Research into meningococcal disease is too fragmented. *BMJ* **318**, 196.

Hoffman, R, G, Nelson, K, and S (1988). Cross-validation of six short forms of the WAIS-R in a healthy geriatric sample. *Journal of Clinical Psychology* **44**, 952-957.

Holt, R. I. G. and Peveler, R. C. (2006). Antipsychotic drugs and diabetes-an application of the Austin Bradford Hill criteria. *Diabetologia* **49**, 1467-1476.

Holthausen, E. A., Wiersma, D., Sitskoom, M. M., Hijiman, R., Dingemans, P. M., Schene, A. H., and van den Bosch, R. J. (2001). Schizophrenic patients without neuropsychological deficits: subgroup, disease severity or cognitive compensation? *Psychiatry Research* **112**, 1-11.

Hoogman, M., van de Beek, D., Weisfelt, M., de Gans, J., and Schman, B. (2007). Cognitive outcome in adults after bacterial meningitis. *J Neurol Neurosurg Psychiatry* doi:10.1136/jnnp.2006.110023, 1-10.

Hopkins, R. O., Weaver, L. K., Pope, D., Orme, J. F., Bigler, E. D., and Larson-LOHR, V. (1999). Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir.Crit Care Med* **160**, 50-56.

Hotopf, M., David, A. S., Hull, L., Nikalaou, V., Unwin, C., and Wessely, S. (2003). Gulf war illness - better, worse, or just the same? A cohort study. *BMJ* **327**, 1378.

Hotopf, M., Noah, N., and Wessely, S. (1996). Chronic fatigue and minor psychiatric morbidity after viral meningitis: a controlled study. *Journal of Neurology, Neurosurgery, and Psychiatry.* **60**, 504-509.

Howard, A. J., Dunkin, K. T., Musser, J. M., and et al. (1991). Epidemiology of *Haemophilus influenzae* type b disease in Wales. *BMJ* **303**, 441-445.

Hubert, B and Caugant, D (1997). Recent changes in meningococcal disease in Europe. *Eurosurveill* **2**, 69-71.

Imrey, P. B., Jackson, L. A., Ludwinski, P. H., England, A. C., III, Fella, G. A., Fox, B. C., Isdale, L. B., Reeves, M. W., and Wenger, J. D. (1995). Meningococcal carriage, alcohol consumption, and campus bar patronage in a serogroup C meningococcal disease outbreak. *J Clin.Microbiol.* **33**, 3133-3137.

Imrey, P. B., Jackson, L. A., Ludwinski, P. H., England, A. C., III, Fella, G. A., Fox, B. C., Isdale, L. B., Reeves, M. W., and Wenger, J. D. (1996). Outbreak of serogroup C meningococcal disease associated with campus bar patronage. *Am.J.Epidemiol.* **143**, 624-630.

Isaacs, E., Christie, D., Vargha-Khadem, F., and Mishkin, M. (1996). Effects of hemispheric side of injury, age at injury, and presence of seizure disorder on functional ear and hand asymmetries in hemiplegic children. *Neuropsychologia* **34**, 127-137.

Isenberg, D. A. and Black, C. (1995). ABC of Rheumatology: Raynaud's Phenomenon, Scleroderma, and Overlap Syndromes. *BMJ* **310**, 795-798.

Jaccard, J. and Wan, C. K. (1996). LISREL approaches to interaction effects in multiple regression. (Sage Publications: Thousand Oaks, CA.)

Jackson, J. C., Hart, R. P., Gordon, S. M., Hopkins, R. O., Girard, T. D., and Ely, E. W. (2007). Post-traumatic stress disorder and post-traumatic stress symptoms following critical illness in medical intensive care unit patients: assessing the magnitude of the problem. *Critical Care* 1-11.

Jackson, L. A., Schuchat, A., Reeves, M. W., and Wenger, J. D. (1995). Serogroup C meningococcal outbreaks in the United States. An emerging threat. *JAMA* **273**, 383-389.

Jadavji, T., Biggar, W. D., Gold, R., and Prober, C. G. (1986). Sequelae of acute bacterial meningitis in children treated for seven days. *Pediatrics* **7**, 21-25.

Jakala, P., Sirvio, J., Riekkinen, M., Koivisto, E., Kejonen, K., Vanhanen, M., and Riekkinen, P. (1999). Guanfacine and clonidine, alpha 2-agonists, improve paired associates learning, but not delayed matching to sample, in humans. *Neuropsychopharmacology* **20** , 119-130.

Jarrold, C., Cowan, N., Hewes, A. K., and Riby, D. M. (2004). Speech timing and verbal short-term memory: Evidence for contrasting deficits in Down syndrome and Williams syndrome. *Journal of Memory and Language* **51**, 365-380.

Javitt, J. C. (1989). When does the failure to find a difference mean that there is none? *Arch Opthalmol* **107**, 1034-1040.

Jenkinson, C., Layte, R, Wright, L, and Coulter, A. The UK SF-36: an analysis and interpretation manual. 1996. Oxford, Health Services Research Unit.
Ref Type: Generic

Jenkinson, C., Stewart-Brown, S., Petersen, S., and Paice, C. (1999). Assessment of the SF-36 version 2 in the United kingdom. *J Epidemiol Commun Health* **53**, 46-50.

Jessor, R., Chase, J. A., and Donovan, J. E. (1980). Psychosocial correlates of marijuana use and problem drinking in a national sample of adolescents. *American Journal of Public Health.* **70**, 604-613.

Johnson, J. H. and Bradlyn, A. S. (1988). Life events and adjustment in childhood and adolescence: Methodological and conceptual issues. In 'In: L.H. Cohen, Editor, *Life Events and Psychological Functioning: Theoretical and Methodological Issues*,'. pp. 64-96. (Sage: Beverly Hills, CA.)

Jones, C., Griffiths, R. D., Macmillan, R., and Palmer, T. E. A. (1994). Psychological problems occurring after intensive care. *British Journal of Intensive Care* 46-53.

Jones, D. (1995). Epidemiology of meningococcal disease in Europe and the USA. In 'Meningococcal Disease'. (Ed. K. Cartwright.) pp. 147-157. (John Wiley & Sons: Chichester.)

Jones, D. M. and Mallard, R. H. (1993). Age incidence of meningococcal infection England and Wales, 1984-1991. *J Infect.* **27**, 83-88.

Jones, I. R., Urwin, G., Feldman, R. A., and Banatvala, N. (1997). Social deprivation and bacterial meningitis in North East Thames region: three year study using small area statistics. *BMJ* **314**, 794-795.

Jones, S. R., Carley, S., and Harrison, M. (2003). An introduction to power and sample size estimation. *Emergency Medicine Journal* **20**, 453-458.

Judge, D., Nadel, S., Vergnaud, S., and Garralda, M. E. (2002). Psychiatric adjustment following meningococcal disease treated on a PICU. *Intensive Care Med.* **28**, 648-650.

Jung, R. E., Yeo, R. A., Chiulli, S. J., Sibbitt, W. L., Weers, D. C, Blaine, L. H., and Brooks, W. M. (1999). Biochemical markers of cognition: a proton MR spectroscopy study of normal human brain. *NeuroReport* **10**, 3327-3331.

Kafetsios, K. and Sideridis, G. D. (2006). Attachment, Social Support and Well-being in Young and Older Adults. *J Health Psychol* **11**, 863-875.

Kaltiala-Heino, R., Rimpela, M., Rantanen, P., and Laippala, P. (2001). Adolescent depression: the role of discontinuities in life course and social support. *Journal of Affective Disorders.* **64**, 155-166.

Kann, L. (2001). The youth risk behaviour surveillance system: Measuring health-risk behaviours. *American Journal of Health Behaviour* **25**, 272-277.

Katz, R. T. and DeLuca, J. (1992). Sequelae of minor traumatic brain injury. *American Family Physician* **46**, 1491-1498.

Kaufman, A. S. (1990). Assessing adolescent and adult intelligence. (Allyn and Bacon Inc.: Boston, MA.)

Kelsey, J. L. (1996). Methods in observational epidemiology. (Oxford University Press: New York.)

Kempton, S., Vance, A., Maruff, P., Luk, E. J., Costin, J., and Pantelis, C. (1999). Executive function and attention deficit hyperactivity disorder: stimulant medication and better executive function performance in children. *Psychological Medicine* **29**, 527-538.

Kessler, R. C. (1987). The interplay of research design strategies and data analysis procedures in evaluating the effects of stress on health. In 'Stress and health: Issues in research methodology'. (S. V. Kasl and C. L. Cooper Eds.) (John Wiley & Sons: Chichester.)

Kiefer, F. (1896). Zur Differential diagnose des Erregens der epidemischen Cerebrospinalmeningitis und der Gonorrhoe. *Berl.Klin.Wochenschr* **33**, 628.

Kirsch, E. A., Barton, R. P., Kitchen, L., and Giroir, B. P. (1996). Pathophysiology, treatment and outcome of meningococcaemia: a review and recent experience. *Pediatr Infect Dis J* **15**, 967-979.

Kish, V. and Lansdown, R. (2000). Meeting the psychological impact of facial disfigurement: developing a clinical service for children and families. *Clinical Child Psychology and Psychiatry* **5**, 497-512.

Klein, J. O., Feigin, R. D., and McCracken, G. H. (1986). Report of the task force on diagnosis and management of meningitis. *Pediatrics* **7**, 959-982.

Klopovich, P., Vats, T. S., Butterfield, G., Cairns, N. U., and Lansky, S. B. (1981). School phobia. *Journal of the Kansas Medical Society* **82**, 125.

Klove, H. (1987). Activation, arousal, and neuropsychological rehabilitation. *Journal of Clinical and Experimental Neuropsychology.* **9**, 297-309.

Kobayashi, H. and Demura, S. (2006). Gender Differences in the Degree of Complaints and Frequency of Subjective Symptoms of Fatigue and Relationships among Their Domains in High School Students. *School Health* **2**, 33-37.

Koenig, H. G., Cohen, H. J., George, L. K., Hays, J. C., Larson, D. B., and Blazer, D. G. (1997). Attendance at religious services, interleukin-6, and other biological parameters of immune function in older adults. *Int J Psychiatry Med* **27**, 233-250.

Kopec JA and Esdaile JM (1990). Bias in case-control studies. A review. *Journal of Epidemiology and Community Health* **44**, 179-186.

Kornelisse, R. F., Westerbeek, C. M. L., and Spoor, A. B. (1995). Pneumococcal meningitis in children: prognostic indicators and outcome. *Clin Infect Dis* **21**, 1390-1397.

Kramer, M. S. (1988). Clinical epidemiology and biostatistics. (Springer-Berlag: New York.)

Krause, G., Blackmore, C., Wiersma, S., Lesneski, C., Woods, C. W., Rosenstein, N. E., and Hopkins, R. S. (2001). Marijuana use and social networks in a community outbreak of meningococcal disease. *South.Med J* **94**, 482-485.

Kremastinou, J., Blackwell, C., Tzanakaki, G., Kallergi, C., Elton, R., and Weir, D. (1994). Parental smoking and carriage of Neisseria meningitidis among Greek schoolchildren. *Scand.J Infect.Dis.* **26**, 719-723.

Kremen, W. S., Seidman, L. J., Faraone, S. V., Pepple, J. R., Lyons, M. J., and Tsuang, M. T. (1995). The '3 Rs' and neuropsychological function in schizophrenia: a test of the matching fallacy in biological relatives. *Psychiatry Res* **56**, 135-143.

Krilov, L. R., Fisher, M., Friedman, S. B., and et al. (1998). Course and outcome of chronic fatigue in children and adolescents. *Pediatrics* **102**, 360-366.

Kristiansen, B. E., Tveten, Y., and Jenkins, A. (1998). Which contacts of patients with meningococcal disease carry the pathogenic strain of Neisseria meningitidis? A population based study. *BMJ* **317**, 621-625.

Kriz, P., Bobak, M., and Kriz, B. (2000). Parental smoking, socioeconomic factors, and risk of invasive meningococcal disease in children: a population based case-control study. *Arch.Dis.Child* **83**, 117-121.

Krizova, P. and Kriz, B. (1999). [Factors affecting the occurrence and development of invasive meningococcal disease and development of Neisseria meningitis carrier state--results of a nationwide prospective questionnaire survey of cases and controls]. *Epidemiol.Mikrobiol.Imunol.* **48**, 140-152.

Laatsch, L. K., Thulborn, K. R., Shobat, CM., and Sweeney, D. M. (2004). Investigating the neurobiological basis of cognitive rehabilitation therapy with fMRI. *Brain Injury* **18**, 957-974.

Landolt, M. A., Vollrath, M., Ribi, K., Gnehm, H. E., and Sennhauser, F. H. (2003). Incidence and associations of parental and child posttraumatic stress symptoms in pediatric patients. *J Child Psychol Psychiatry* **44**, 1199-1207.

Lang, H. G. (2002). Higher Education for Deaf Students: Research Priorities in the New Millennium. *Journal of Deaf Studies and Deaf Education* **7**, 267-280.

Lapeyssonnie, L. (1963). La meningite cerebro-spinale en Afrique. *Bull WHO* **28**, 3-114.

Laupland, K. B., Davies, H. D., and Kellner, J. D. (1998). Predictors and outcome of admission for invasive Streptococcus pneumoniae infections at a Canadian children's hospital. *Clin Infect Dis* **27**, 597-602.

Leib, S. L. and Tauber, M. G. (1999). Pathogenesis of bacterial meningitis. *Infect Dis Clin North Am* 527-548 vi-vi.

Leininger, B. E., Gramling, S. E., and Farrell, A. D. (1991). Neuropsychological deficits in symptomatic minor head injury patients after concussion and mild concussion. *Journal of Neurology, Neurosurgery, and Psychiatry.* **53**, 293-296.

Leowski, J. (1986). Mortality from acute respiratory infections in children under 5 years of age: global estimates. *World Health Stat.Q.* **39**, 138-144.

Levitt, L. P., Bond, J. O., Hall, I. E., Jr., Dame, G. M., Buff, E. E., Marston, C., and Prather, E. C. (1970). Meningococcal and ECHO-9 meningitis. Report of an outbreak. *Neurology* **20**, 45-51.

Levy, J. (1972). Lateral specialization of the brain: Behavioural manifestations and possible evolutionary basis. In 'The biology of behaviors'. (Ed. J. A. Kiger.) (Oregon State Press: Corvallis, OR.)

Lewinsohn, P. M., Roberts, R. E., Seeley, J. R., Rohde, P., Gotlib, I. H., and Hops, H. (1994). Adolescent psychopathology: II Psychosocial risk factors for depression. *Journal of Abnormal Psychology* **103**, 302-315.

Lewinsohn, P. M., Rohde, P., and Seeley, J. R. (1998). Major depressive disorder in older adolescents: prevalence, risk factors, and clinical implication. *Clinical Psychology Review* **18**, 765-794.

Lezak, M. D. (1995). Neuropsychological Assessment. (Oxford University Press, Inc.: New York.)

Lin, V. H., Parekh, R. S., McQuillan, M. A., Braun, D. K., and Markovitz, D. M. (1995). Meningococcal endocarditis presenting as cellulitis. *Clin.Infect.Dis.* **21**, 1023-1025.

Lingappa, J. R., Al Rabeah, A. M., Hajjeh, R., Mustafa, T., Fatani, A., Al Bassam, T., Badukhan, A., Turkistani, A., Makki, S., Al Hamdan, N., Al Jeffri, M., Al Mazrou, Y., Perkins, B. A., Popovic, T., Mayer, L. W., and Rosenstein, N. E. (2003). Serogroup W-135 meningococcal disease during the Hajj, 2000. *Emerg. Infect.Dis.* **9**, 665-671.

Loge, J. H., Ekeberg, O., and Kaasa, S. (1998). Fatigue in the general population: normative data and associations. *J Psychosom Res* **45**, 53-65.

Loring, D. W., Lee, G. P., Martin, R. C., and Meador, K. J. (1988). Material-specific learning in patients with complex partial seizures of temporal lobe origin. Convergent validation of memory constructs. *Journal of Epilepsy* **15**, 53-59.

Louis, W. J., Mander, A. G., Dawson, M., O'Callaghan, C., and Conway, E. L. (1999). Use of computerized neuropsychological tests (CANTAB) to assess cognitive effects of antihypertensive drugs in the elderly. Cambridge Neuropsychological Test Automated Battery. *Journal of Hypertension* **17**, 1813-1819.

Luciana, M. and Melson, C. A. (1998). The functional emergence of prefrontally-guided working memory systems in four- to eight-year-old children. *Neuropsychologia* **36**, 273-293.

Macartney-Filgate, M. S. and Vriezen, E. R. (1988). Interrcorrelation of clinical tests of verbal memory. *Archives of Clinical Neuropsychology* **3**, 121-126.

MacLennan, J., Kafatos, G., Neal, K., Andrews, N., Cameron, C., Roberts, R., Evans, M. R., Cann, K., Baxter, D. N., Maiden, M., and Stuart, J. (2006). Social behaviour and Meningococcal Carriage in British Teenagers. *Emerg Infect Dis* **12**, 950-957.

MacMahon, B. and Pugh, T. F. (1970). Epidemiology: Principles and Methods. (Little, Brown: Boston.)

Maiden, M. C., Bygraves, J. A., Feil, E., Morelli, G., Russell, J. E., Urwin, R., Zhang, Q., Zhou, J., Zurth, K., Caugant, D. A., Feavers, I. M., Achtman, M., and Spratt, B. G. (1998). Multilocus sequence typing: a portable approach to the identification of clones within populations of pathogenic microorganisms. *Proc. Natl. Acad Sci U.S.A* **95**, 3140-3145.

Mann, C. J. (2003). Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emerg med J* **20**, 54-60.

Marchiafava, E. and Celli, A. (1884). Spra i micrococchi della meningite cerebrospinale epidemica. *Gazz degli Ospedali* **5**, 59.

Marks, M. I., Frasch, C. E., and Shapera, R. M. (1979). Meningococcal colonization and infection in children and their household contacts. *Am J Epidemiol.* **109**, 563-571.

Marschark, M. (2007). Raising and educating a deaf child: A comprehensive guide to the choices, controversies, and decisions faced by parents and educators. (Oxford University Press.: New York.)

Marsh, H. (1990). The causal order of academic self-concept and academic achievement: A multiwave, longitudinal path analysis. *Journal of Educational Psychology* **82**, 646-656.

Martin, A. and Cohen, D. J. (2000). Adolescent depression: Window of (missed?) opportunity. *American Journal of Psychiatry* **10**, 1549-1551.

Martin, D. R., Walker, S. J., Baker, M. G., and Lennon, D. R. (1998). New Zealand epidemic of meningococcal disease identified by a strain with phenotype B:4:P1.4. *J.Infect.Dis.* **177**, 497-500.

Martis, B., Alam, D., Dowd, S. M., Hill, S. K., Sharma, R. P., Rosem, C., Pliskin, N., Martin, E., Carson, V., and Janicak, T. Neurocognitive effects of repetitive transcranial magnetic stimulation in severe major depression. Clinical Neurophysiology 114, 1125-1132. 2003.

Masanic, C. A., Bayley, M. T., van Reekum, R., and Simard, M. (2001). Open-Label Study of Donepezil in Traumatic Brain Injury. *Arch Phys Med Rehabil* **82**, 896-901.

Mayer, L. W., Reeves, M. W., Al Hamdan, N., Sacchi, C. T., Taha, M. K., Ajello, G. W., Schmink, S. E., Noble, C. A., Tondella, M. L., Whitney, A. M., Al Mazrou, Y., Al Jefri, M., Mishkhis, A., Sabban, S., Caugant, D. A., Lingappa, J., Rosenstein, N. E., and Popovic, T. (2002). Outbreak of W135 meningococcal disease in 2000: not emergence of a new W135 strain but clonal expansion within the electrophoretic type-37 complex. *J Infect.Dis.* **185**, 1596-1605.

Mazza, J. and Reynolds, W. (1998). A longitudinal investigation of depression, hopelessness, social support, and major and minor life events and their relation to suicidal ideation in adolescents. *Suicide and Life-Threatening Behaviour* **28**, 358-374.

McCabe, R. J. R. and Green, D. (1987). Rehabilitation of severely head-injured adolescents: three case reports. *Journal of Child Psychology and Psychiatry* **28**, 111-126.

McCubbin, H. and Patterson, J. (1983). Stress: Family inventory of life events and changes. In '*A Sourcebook of Marriage and Family Assessment.*'. (Ed. E. Filsinger.) (Sage: Beverly Hills, CA.)

McCubbin, H. and Thompson, A. I. (1991). Family assessment inventories for research and practice. (University of Wisconsin: Madison, WI.)

McCubbin, H. I., Patterson, J. M., Bauman, E., and Harris, L. H. (1982). Adolescent-Family Inventory of Life Events and Changes. In 'In D. H. Olson, H. I. McCubbin, H. Barnes, A. Larsen, M. Muxen, & M. Wilson (Eds.), Family inventories.'. pp. 128-142. (St. Paul: University of Minnesota Press.:

McCullough, M. E., Hoyt, W. T., Larson, D. B., Koenig, H. G., and Thoresen, C. (2000). Religious involvement and mortality: a meta-analytic review. *Health Psychol* **19**, 211-222.

McManus, I, C, &, Mascie-Taylor, C, G, and N (1983). Biosocial correlates of cognitive abilities. *Journal of Biosocial Science* **15**, 289-306.

McManus, I, C, Shergill, S, &, Bryden, and M P (1993). Annett's theory that individuals heterozygous for the right shift gene are intellectually advantaged: Theoretical and empirical problems. *Journal of Psychology* **84**, 517-537.

Meningococcal Disease Surveillance Group (1974). Meningococcal disease: secondary attack rate and chemoprophylaxis in the United States. *JAMA* **235**, 261-265.

Meningococcal Reference Unit. Newsletter HPA North West Regional Laboratory December 2005. Issue 1, 3. 2005.

Merkelbach, H., Sittinger, I., Schweizer, I., and Muller, M. (2000). Cognitive outcome after bacterial meningitis. *Acta Neurol Scand* **102**, 118-123.

Meyers, J. E. and Lange, D. (1994). Recognition Subtest for the Complex Figure. *The Clinical Neuropsychologist* **8**, 153-166.

Miettinen, O. S. (1985). Theoretical Epidemiology. Principles of Occurrence Research in Medicine. (John Wiley & Sons: New York.)

Milagres, L. G., Ramos, S. R., Sacchi, C. T., Melles, C. E., Vieira, V. S., Sato, H., Brito, G. S., Moraes, J. C., and Frasch, C. E. (1994). Immune response of Brazilian children to a Neisseria meningitidis serogroup B outer membrane protein vaccine: comparison with efficacy. *Infect.Immun.* **62**, 4419-4424.

Miller, E., Salisbury, D., and Ramsay, M. (2001). Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story. *Vaccine* **20 Suppl 1**, S58-S67.

Milner, B. (1971). Interhemispheric differences in the localisation of psychological processes in man. *Br Med Bull* **27**, 272-277.

Milner, B. (1975). Psychological aspects of focal epilepsy and its neurobiological management. *Adv Neurol* **8**, 299-321.

Missar, C, D, Gold, J, M, Goldberg, T, and E (1994). WAIS-R short forms in chronic schizophrenia. *Schizophrenia Research* **12,** 247-250.

Miyahara, M. and Piek, J. (2006). Self-Esteem of Children and Adolescents with Physical Disabilities: Quantitative Evidence from Meta-Analysis. *Journal of Developmental and Physical Disabilities* **18**, 219-234.

Mockler, D., Riordan, J., and Sharma, T. (1996). A comparison of the NART (restandardized) and the NART-R (revised). *British Journal of Clinical Psychology* **35**, 567-572.

Monden, S. (1990). Relationship between subjective symptoms of fatigue and living behavior in senior high school students: A study by quantification method II. *Jpn J School Health* **32**, 239-247.

Monroe, S. M. and Peterman, A. M. (1988). Life stress and psychopathology. In 'Life Events and Psychological Functioning: Theoretical and Methodological Issues.'. pp. 31-63. (Sage: Beverly Hills, CA .)

Moodley, J. R., Coetzee, N., and Hussey, G. (1999). Risk factors for meningococcal disease in Cape Town. *S.Afr.Med J* **89**, 56-59.

Moore, J. L., McAuley, J. W., Long, L., and Bornstein, R. (2002). An evaluation of the effects of methylphenidate on outcomes in adult epilepsy patients. *Epilepsy Behavior* **3**, 92-95.

Moore, P. S., Hierholzer, J., DeWitt, W., Gouan, K., Djore, D., Lippeveld, T., Plikaytis, B., and Broome, C. V. (1990). Respiratory viruses and mycoplasma as cofactors for epidemic group A meningococcal meningitis. *JAMA* **264**, 1271-1275.

Moore, P. S., Reeves, M. W., Schwartz, B., Gellin, B. G., and Broome, C. V. (1989). Intercontinental spread of an epidemic group A Neisseria meningitidis strain. *Lancet* **2**, 260-263.

Morley, S. L. and Booy, R. (1997). Epidemiology and prevention of meningococcal disease. *Current Paediatrics* **7**, 1-6.

Morley, S. L. and Pollard, A. J. (2001). Vaccine prevention of meningococcal disease, coming soon? *Vaccine* **20**, 666-687.

Morris, R. G., Worsley, C., and Matthews, D. (2000). Neuropsychological assessment in older people: old principle and new directions. *Advances in Psychiatric Treatment* **6**, 362-372.

Moss, A. R. and Dowd, T. (1991). Does the NART hold after head injury: a case report. *Br J Clin Psychol* **30**, 179-180.

Moss, P. (1982). The outcome of meningococcal group B meningitis. *Arch Dis Child* **57**, 616-621.

Mothershed, E., Besser, J., and Perkins, B. (2001). Evaluation of pulsed-field gel electrophoresis in epidemiological investigations of meningococcal disease outbreaks caused by Neisseria meningitidis serogroup C. *J Clin Microbiol* **39**, 75-85.

Mueller, J. E., Borrow, R., and Gessner, B. D. (2006). Meningococcal serogroup W135 in the African meningitis belt: epidemiology, immunity and vaccines. *Expert. Rev Vaccines.* **5**, 319-336.

Mulholland, K., Hilton, S., Adegbola, R., and et al (1997). Randomised trial of Haemophilus influenzae type-b tetanus protein conjugates for prevention of pneumonia and meningitis in Gambia infants. *Lancet* **349**, 1191-1197.

Murray, B. L., Kenardy, J. A., and Spence, S. H. (2008). Brief Report: Children's Responses to Trauma - and Non-trauma-related Hospital Admission: A Comparison Study. *J Pediatr Psychol* **33**, 435-440.

Mustafa, M. M., Mertsola, J., Ramilo, O., Saez-Llorens, X., Risser, R. C., and McCracken, G. H., Jr. (1989). Increased endotoxin and interleukin-1 beta concentrations in cerebrospinal fluid of infants with coliform meningitis and ventriculitis associated with intraventricular gentamicin therapy. *J Infect.Dis.* **160**, 891-895.

Nadel, S. (2001). Lumbar puncture should not be performed in meningococcal disease. *Arch.Dis.Child* **84**, 375.

Nadel, S., Britto, J., Booy, R., Maconochie, I., Habibi, P., and Levin, M. (1998). Avoidable deficiencies in the delivery of health care to children with meningococcal disease. *J Accid.Emerg.Med* **15**, 298-303.

Nadel, S., Levin, M., and Habibi, P. (1995). Treatment of meningococcal disease in childhood. In 'Meningococcal Disease'. (Ed. K. Cartwright.) pp. 207-243. (John Wiley and Sons, Chichester.)

Naess, A., Halstensen, A., Nyland, H., Pedersen, S. H., Moller, P., Borgmann, R., Larsen, J. L., and Haga, E. (1994). Sequelae one year after meningococcal disease. *Acta Neurol Scand.* **89**, 139-142.

Nassif, X., Bourdoulous, S., Eugene, E., and Couraud, P. O. (2002). How do extracellular pathogens cross the blood-brain barrier? *Trends Microbiol.* **10**, 227-232.

Nassif, X. and So, M. (1995). Interaction of pathogenic Neisseria with nonphagocytic cells. *Clin Microbiol.Rev.* **8**, 376-388.

Nau, R. and Bruck, W. (2002). Neuronal injury in bacterial meningitis: mechanisms and implications for therapy. *Trends Neurosci* **25**, 38-45.

Neal, K. R., Nguyen-Van-Tam, J. S., Jeffrey, N., Slack, R. C., Madeley, R. J., Ait-Tahar, K., Job, K., Wale, M. C., and Ala'Aldeen, D. A. (2000). Changing carriage rate of Neisseria meningitidis among university students during the first week of term: cross sectional study. *BMJ* **320**, 846-849.

Nelson, H, E, and O'Connell. Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. C 14, 234-244. 1978.
Ref Type: Journal (Full)

Nelson, H. E. and Willison, J. R. The revised national adult reading test - test manual. 2nd. 1991. Windsor, The NFER-Nelson Publishing Company. 1991.

Nelson, S. J., Charlett, A., Orr, H. J., Barker, R. M., Neal, K. R., Taylor, C., Monk, P. N., Evans, M. R., and Stuart, J. M. (2001). Risk factors for meningococcal disease in university halls of residence. *Epidemiol.Infect.* **126**, 211-217.

Neuman, H. B. and Wald, E. R. (2001). Bacterial meningitis in childhood at the Children's Hospital of Pittsburgh: 1988-1998. *Clin Pediat* **40**, 595-600.

Neville, K (1998). The relationships among uncertainty, social support, and psychological distress in adolescents recently diagnosed with cancer. *Journal of Pediatric Oncology Nursing,* **15**, 37-46.

Nielen, M. M. and Boer, J. A. (2003). Neuropsychological performance of OCD patients before and after treatment with fluoxetine: Evidence for persistent cognitive deficits. *Psychological Medicine* **33**, 917-925.

Ninis, N., Phillips, C., Bailey, L., Pollock, J. I., Nadel, S., Britto, J., Maconochie, I., Winrow, A., Coen, P. G., Booy, R., and Levin, M. (2005). The role of healthcare delivery in the outcome of meningococcal disease in children: case-control study of fatal and non-fatal cases. *BMJ* **330**, 1475.

Nir, Y. (1985). Post-traumatic stress disorder in children with cancer. In S. Eth and R. Pynoos (Eds.). Post-traumatic stress children with cancer. In 'In S. Eth and R. Pynoos (Eds.). Post-traumatic stress disorders in children.'. pp. 123-132. (American Psychiatric Press.: Washington, DC.)

Nolen-Hoeksema, S. and Girgus, J. S. (1994). The emergence of gender differences in depression. *Psychol Bull* **115**, 424-443.

Norgard, B., Sorensen, H. T., Jensen, E. S., Faber, T., Schonheyder, H. C., and Nielsen, G. L. (2002). Pre-hospital parenteral antibiotic treatment of meningococcal disease and case fatality: a Danish population-based cohort study. *J Infect.* **45**, 144-151.

Noronha, C. P., Struchiner, C. J., and Halloran, M. E. (1995). Assessment of the direct effectiveness of a BC meningococcal vaccine in Rio Janeiro, Brazil: A case-control study. *Int J Epidemiol* **24**, 1050-1057.

Northam, E. A., Anderson, P. J., Jacobs, R., Hughes, M., Warne, G. L., and Werther, G. A. (2001). Neuropsychological profiles of children with Type 1 diabetes 6 years after disease onset. *Diabetes Care* **24**, 1541-1546.

Nuckolls, K. B., Cassel, J., and Kaplan, B. H. (1972). Psychosocial Assets, Life Crises, and the Prognosis of Pregnancy. *American Journal of Epdemiology* **95**, 431-441.

Nunnally, J. C. and Berstein, I. H. (1994). Psychometric Theory. (McGraw-Hill Inc.: New York, NY.)

O'Brien, K. and Morton, N. S. (1998). Haemodynamic improvement in a child with meningococcal sepsis following methylprednisolone: restoration of beta-adrenergic receptor responsiveness? *Paediatr.Anaesth.* **8**, 419-420.

O'Brien, M. and Jones, D. (2001). Children, parental employment and educational attainment. *Cambridge Journal of Economics,* **23**, 599-621.

O'Carroll, R. (1995). The assessment of premorbid ability: a critical review. *Neurocase* **1**, 83-89.

O'Carroll, R. E. (1987). The inter-rater reliability of the National Adult Reading Test (NART): a pilot study. *British Journal of Clinical Psychology* **26**, 229-230.

Odegaard, A. (1983). Unusual manifestations of meningococcal infection. A review. *NIPH Ann* **6**, 59-63.

Odio, C. M., Faingezicht, I., Paris, M., Nassar, M., Baltodano, A., Rogers, J., Saez-Llorens, X., Olsen, K. D., and McCracken, G. H., Jr. (1991). The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis 1. *N Engl.J Med* **324**, 1525-1531.

Ohring, R., Graber, J. A., and Brooks-Gunn, J. (2002). Girls' recurrent and concurrent body dissatisfaction: correlates and consequences over 8 years. *Int J Eat Disord* **31**, 404-415.

Olson, S. H., Voigt, L. F., Begg, C. B., and Weiss, N. S. (2002). Reporting participation in case-control studies. *Epidemiology* **13**, 123-126.

Osman, A., Downs, W. R., Barrios, F. X., Kopper, B. A., Gutierrez, P. M., and Chiros, C. E. (1997). Factor structure and psychometric characteristics of the Beck Depression Inventory–II. *Journal of Psychopathology and Behavioral Assessment,* **19**, 359-376.

Osterrieth, P. A. (1944). Le test du copie d'une figure complexe. *Archives of Psychology* **30**, 206-356.

Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E., and Robbins, T. W. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia* **28**, 1021-1034.

Owen, A. M., James, M., Leigh, P. N., Summers, B. A., Marsden, C. D., Quinn, N. P., Lange, K. W., and Robbins, T. W. (1992). Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain* **115**, 1727-1751.

Owen, A. M., Roberts, A. C., Polkey, C. E., Sahakian, B. J., and Robbins, T. W. (1991). Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia* **29**, 993-1006.

Owen, A. M., Sahakian, B. J., Semple, J., Polkey, C. E., and Robbins, T. W. (1995). Visuospatial short-term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia* **33**, 1-24.

Oxford Centre for Evidence-Based Medicine. Cohort Studies. Accessed: July 25, 2007.

Packham, J. C. and Hall, M. A. (2002). Long-term follow-up of 246 adults with juvenile idiopathic arthritis: social function, relationships and sexual activity. *Rheumatology* **41**, 1443.

Pantelis, C., Barnes, T. R. E., Nelson, H. E., Tanner, S., Weatherley, L., Owen, A. M., and Robbins, T. W. (1997). Frontal-striatal cognitive deficits in-patients with chronic schizophrenia. *Brain* **120**, 1823-1824.

Patel, V., Flisher, A. J., Hetrick, S., and McGorry, P. (2007). Mental health of young people: a global public-health challenge. *The Lancet* **369**, 1302-1313.

Pathan, N., Faust, S. N., and Levin, M. (2003). Pathophysiology of meningococcal meningitis and septicaemia. *Arch.Dis.Child* **88**, 601-607.

Patrick, D. L., Danis, M., Southerland, L. J., and Hong, G. (1988). Quality of life following intensive care. *J Gen Int Med* **3**, 218-223.

Pawlikowska, T., Chalder, T., Hirsch, S. R., Wallace, P., Wright, D. J., and Wessely, S. C. (1994). Population based study of fatigue and psychological distress. *BMJ* **308**, 763-766.

Paykel, E. S. (1994). Life events, social support and depression. *Acta Psychiatr.Scand.Suppl* **377**, 50-58.

Pelcovitz, D., Goldenberg, B., and Kaplan, S. (1996). Posttraumatic stress disorder in mothers of paediatric cancer survivors. *Psychosomatics.* **37**, 116-126.

Perneger, T. V. (1998). What's wrong with Bonferroni adjustments. *BMJ* **316**, 1236-1238.

Pether, J. V., Lightfoot, N. F., Scott, R. J., Morgan, J., Steele-Perkins, A. P., and Sheard, S. C. (1988). Carriage of Neisseria meningitidis: investigations in a military establishment. *Epidemiol.Infect.* **101**, 21-42.

Petito, F. and Cummins, R. A. (2000). Quality of life in adolescence: The role of perceived control, parenting style, and social support. *Behav Change* **17**, 196-207.

Piko, B. (1998). Social support and health in adolescence: A factor analytical study. *British Journal of Health Psychology* **3**, 333-344.

Pizzamiglio, L., Perani, D., and Cappa, S. (1998). Recovery of neglect after right hemisphere damage. *Arch Neurol* **55**, 561-568.

Pocock, S. J. (1983). Clinical Trials: A Practical Approach. (Wiley: New York.)

Pollard, A. J. and Levin, M. (2000). Vaccines for prevention of meningococcal disease. *Pediatr.Infect.Dis.J* **19**, 333-344.

Pomeroy, S. L., Holmes, S. J., Dodge, P. R., and Feigin, R. D. (1990). Seizures and other neurological sequelae of bacterial meningitis in children. *N Engl J Med* **323**, 1651-1657.

Ponsford, J. and Kinsella, G. (1992). Attentional deficits following closed head injury. *Journal of Clinical and Experimental Neuropsychology* **14**, 822-838.

Poolman, J. T. (1995). Development of a meningococcal vaccine. *Infect.Agents Dis.* **4**, 13-28.

Popovic, T., Sacchi, C. T., Reeves, M. W., Whitney, A. M., Mayer, L. W., Noble, C. A., Ajello, G. W., Mostashari, F., Bendana, N., Lingappa, J., Hajjeh, R., and Rosenstein, N. E. (2000). Neisseria meningitidis serogroup W135 isolates associated with the ET-37 complex. *Emerg.Infect.Dis.* **6**, 428-429.

Prado, G., Szapocznik, J., Mitrani, V. B., Mauer, M. H., Smith, L., and Feaster, D. (2002). Factors Influencing Engagement into Interventions for Adaptation to HIV in African American Women. *AIDS Behav.2002 June; 6(2): 141-151.* **6**, 141-151.

Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre. Facts & Figures. 19-2-2001. PHLS.

Public Health Laboratory Service Meningococcus Forum. (2002). Guidelines for Public Health Management of Meningococcal Disease in the UK. *Communicable Disease and Public Health.* **5**, 187-204.

Pugh, K. G., Kieley, D. K., Milberg, W. P., and Lipsitz, L. A. (2003). Selective impairment of frontal-executive cognitive function in African Americans with cardiovascular risk factors. *J Am Geriatr* **51**, 1439-1444.

Puura, K., Almqvist, J., Piha, I., and Moilanen, T. (1998). Children with symptoms of depression - What do adults see? *Journal of Child Psychology and Psychiatry and Allied Disciplines.* **39**, 577-585.

Racoosin, J. A., Whitney, C. G., Conover, C. S., and Diaz, P. S. (1998). Serogroup Y meningococcal disease in Chicago, 1991-1997. *JAMA* **280**, 2094-2098.

Raghunathan, P. L., Jones, J. D., Tiendrebeogo, S. R., Sanou, I., Sangare, L., Kouanda, S., Dabal, M., Lingani, C., Elie, C. M., Johnson, S., Ari, M., Martinez, J., Chatt, J., Sidibe, K., Schmink, S., Mayer, L. W., Konde, M. K., Djingarey, M. H., Popovic, T., Plikaytis, B. D., Carlone, G. M., Rosenstein, N., and Soriano-Gabarro, M. (2006). Predictors of immunity after a major serogroup W-135 meningococcal disease epidemic, Burkina Faso, 2002. *J Infect Dis* **193**, 607-616.

Ragunathan, L., Ramsay, M., Borrow, R., Guiver, M., Gray, S., and Kaczmarski, E. B. (2000). Clinical features, laboratory findings and management of meningococcal meningitis in England and Wales: report of a 1997 survey. Meningococcal meningitis: 1997 survey report. *J Infect.* **40**, 74-79.

Rait, D., Ostroff, J., Smith, K., Cella, D., Tan, C., and Lesko, L. (1992). Perceived family functioning and the psychosocial adjustment of adolescent cancer survivors. *Family Process,* **31**, 383-397.

Ramsay, M, Kaczmarski, E, Rush, M, Mallard, R, Farrington, P, and White, J (1997). Changing patterns of case ascertainment and trends in meningococcal disease in England & Wales. *Commun Dis Rep CDR Rev* **7**, R49-54.

Ramsay, M. E., Andrews, N., Kaczmarski, E. B., and Miller, E. (2001). Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. *Lancet* **357**, 196-197.

Ramsay, M. E., Andrews, N. J., Trotter, C. L., Kaczmarski, E. B., and Miller, E. (2003). Herd immunity from meningococcal serogroup C conjugate vaccination in England: database analysis. *BMJ* **326**, 365-366.

Ravert, A. A. and Martin, J. (1997). Family stress, perception of pregnancy and age at first menarche among pregnant adolescents. *Adolescence* **32**, 261-269.

Rayner, C. F., Dewar, A., Moxon, E. R., Virji, M., and Wilson, R. (1995). The effect of variations in the expression of pili on the interaction of Neisseria meningitidis with human nasopharyngeal epithelium. *J Infect.Dis.* **171**, 113-121.

Raza, M. W., El Ahmer, O. R., Ogilvie, M. M., Blackwell, C. C., Saadi, A. T., Elton, R. A., and Weir, D. M. (1999). Infection with respiratory syncytial virus enhances expression of native receptors for non-pilate Neisseria meningitidis on HEp-2 cells. *FEMS Immunol.Med.Microbiol.* **23**, 115-124.

Rea, T. D., Russo, J. E., Katon, W., Ashley, R. L., and Buckwald, D. S. (2001). Prospective study of the natural history of infectious mononucleosis caused by Epstein-Barr virus. *J Am Board Fam Pract* **14**, 234-242.

Rees, G., Gledhill, J., Garralda, M. E., and Nadel, S. (2004). Psychiatric outcome following paediatric intensive care unit (PICU) admission: a cohort study. *Intensive Care Med* **30**, 1607-1614.

Reid, M., Glazener, C., Murray, G. D., and Taylor, G. S. (2002). A two-centred pragmatic randomised controlled trial of two interventions of postnatal support. *An International Journal of Obstetrics and Gynaecology* **109**, 1164-1170.

Rey, A. (1941). L'examen psychologique dans les cas d'encephalopathie traumatique. *Archives of Psychology* **28**, 286-340.

Rey, A. (1964). L'examen clinique en psychologie. (Presses Universitaires de France: Paris.)

Richman, J., Rosenfield, L., and Bowen, G. (1998). Social support for adolescents at risk of school failure. *Social Work* **43**, 309-323.

Richmond, P., Borrow, R., Miller, E., Clark, S., Sadler, F., Fox, A., and et al (1999). Meningococcal serogroup C conjugate vaccine is immunogenic in infancy and primes for memory. *J Infect Dis* **17**, 1569-1572.

Riordan, F. A., Marzouk, O., Thomson, A. P., Sills, J. A., and Hart, C. A. (1995). The changing presentations of meningococcal disease. *Eur.J Pediatr.* **154**, 472-474.

Riordan, T., Cartwright, K., Andrews, N., Stuart, J., Burris, A., Fox, A., Borrow, R., Douglas-Riley, T., Gabb, J., and Miller, A. (1998). Acquisition and carriage of meningococci in marine commando recruits. *Epidemiol Infect* **121**, 495-505.

Robbins, J. B., Schneerson, R., Anderson, P., and Smith, D. H. (1996). Prevention of systemic infections, especially meningitis caused by Haemophilus influenzae type b. Impact on public health and implications for other polysaccharide-based vaccines. *JAMA* **276**, 1181-1185.

Robbins, T. W., James, M., Owen, A. M, Shakaian, B. J., Lawrence, A. D., McInnes, L., and Rabbitt, P. (1998). A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: Implications for theories of executive functioning and cognitive aging. *Journal of the International Neuropsychological Society* **4**, 474-490.

Robbins, T. W., James, M., Owen, A. M., Sahakian, B, McInnes, L., and Rabbitt, P. (1994). Cambridge Neuropsychological Test Automated Battery (CANTAB): A factor analytic study of a large sample of normal elderly volunteers. *Dementia* **5**, 266-281.

Robinson, P., Taylor, K., and Nolan, T. (2001). Risk-factors for meningococcal disease in Victoria, Australia, in 1997. *Epidemiol.Infect.* **127**, 261-268.

Roos, K. L., Tunkel, A. R., and Scheld, W. M. (1997). Acute bacterial meningitis in children and adults. In 'Infections of the Central Nervous System'. (W. M. Scheld, R. J. Whitley, and D. T. Durack Eds.) pp. 335-401. (Lippincott-Raven: Philadelphia, PA.)

Rosenberg, M. (1986). Self-concept from middle childhood through adolescence. *Psychological Perspectives on the Self* **3**, 107-136.

Rosenstein, N. E. and Perkins, B. A. (2000). Update on Haemophilus influenzae serotype b and meningococcal vaccines. *Pediatr.Clin.North Am.* **47**, 337-52, vi.

Rosenstein, N. E., Perkins, B. A., Stephens, D. S., Lefkowitz, L., Cartter, M. L., Danila, R., Cieslak, P., Shutt, K. A., Popovic, T., Schuchat, A., Harrison, L. H., and Reingold, A. L. (1999). The changing epidemiology of meningococcal disease in the United States, 1992-1996. *J Infect.Dis.* **180**, 1894-1901.

Rosenstein, N. E., Perkins, B. A., Stephens, D. S., Popovic, T., and Hughes, J. M. (2001). Meningococcal disease. *N.Engl.J.Med.* **344**, 1378-1388.

Rothman, K. J. (1986). Modern Epidemiology. (Little, Brown & Co: Boston.)

Rothman, K. J. and Greenland, S. (1998). Precision and validity in epidemiologic studies. In 'Modern Epidemiology. Vol. 2'. (Rothman KJ and Greenland SEds.) pp. 115-134. (Lippincott, Williams & Wilkins: Philadelphia, PA.)

Royal College of Paediatrics and Child Health. Bridging the Gaps: Health Care for Adolescents. CR114. 2003. Royal College of Psychiatrists Council Report .

Rutter, M. (1985). Resilience in the Face of Adversity: Protective Factors and Resistance to Psychiatric Disorder. *British Journal of Psychiatry* **147**, 598-611.

Rutter, M. (1986). The Developmental Psychopathology of Depression Issues and Perspectives. In 'Depression in Young People: Developmental and Clinical Perspectives.'. (Ed. Michael Rutter) pp. 3-30. (Guilford.: New York.)
Sackett, D. L. (1979). Bias in analytic research. *J Chronic Dis* **32**, 51-63.

Sacks, H. S. (1986). Meningococcal pneumonia and empyema. *Am J Med* **80**, 290-291.

Saez-Llorens, X. and McCracken, G. H. (1990). Bacterial meningitis in neonates and children. *Infect Dis Clin North Am* **4**, 623-644.

Sahakian, B, Morris, R. G., Evenden, J. L., Heald, A., Levy, R., Philpot, M. P., and Robbins, T. W. (1988). A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. *Brain* **111**, 695-718.

Sahakian, B. and Owen, A. (1992). Computerised assessment in neuropsychiatry using CANTAB. *J R Soc Med* **85**, 399-402.

Saigh, P. A., Mroueh, M. N., and Bremmer, J. D. (1997). Scholastic impairments among traumatized adolescents. *Behaviour Research & Therapy* **35**, 429-436.

Salisbury, D. M. (1998). Summary statement: The first international conference on Haemophilus influenzae type b infection in Asia. *Pediatr Infect Dis J* **17**, S93-S95.

Sander, J., Bay, D., Gedde-Dahl, T. W., Borchgrevink, H. M., Froholm, L. O., Oftedal, S. I., and Vandvik, B. (1984). Late sequelae after meningococcal disease. A controlled study in young men. *NIPH Ann.* **7**, 3-11.

Sander, J., Host, J. H., Gedde-Dahl, T. W., Bay, D., Borchgrevink, H. M., Froholm, L. O., Oftedal, S. I., and Vandvik, B. (1984). Late sequelae after meningococcal disease as related to anamnestic and clinical factors recorded during the acute illness. *NIPH Ann.* **7**, 69-82.

Santrock, J. W. (2002). Life-span development. (McGraw Hill: Boston.)

Sarason, B. R., Sarason, I. G., and Pierce, G. R. (1990). Social Support: An Interactional View. (John Wiley & Sons.: New York.)

Sarason, B. R., Sarason, I. G., Shearin, E. N., and Pierce, R. (1987). A Brief Measure of Social Support: Practical and Theoretical Implications. *Journal of Social and Personal Relationships* **4**, 497-510.

Sarason, I. G., Levine, H. M., Basham, R. B., and Sarason, B. R. (1983). Assessing Social Support: The Social Support Questionnaire. *Journal of Personality and Social Psychology.* **44**, 127-139.

Sattler J.M. (1988). Assessment of Children's Intelligence. San Diego, CA.)

Schaad, U. B. (1980). Arthritis in disease due to Neisseria meningitidis. *Rev Infect Dis* **2**, 880-888.

Schaad, U. B., Kaplan, S. L., and McCracken, G. H., Jr. (1995). Steroid therapy for bacterial meningitis. *Clin Infect.Dis.* **20**, 685-690.

Schaeffer, C. M., Alexander, P. C., Bethke, K., and Kretz, L. S. (2005). Predictors of Child Abuse Potential Among Military Parents: Comparing Mothers and Fathers. *Journal of Family Violence* **20**, 123-129.

Scheibel, M. E. and Scheibel, A. B. (1958). Structural substrates for integrative pattern in the brain stem reticular core. In 'Reticular Formation of the Brain'. (H. H. Jasper and L. D. Proctor Eds.) pp. 31-55. (Henry Ford Hospital International Symposium.: Little Brown, Boston.)

Schelling, G., Briegel, J., Roozendaal, B., Stoll, C., Rothenhausler, H. B., and Kapfhammer, H. P. (2001). The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. *Biol Psychiatry* **50**, 978-985.

Schlesselman, J. J. (1987). Proof of cause and effect in epidemiologic studies: Criteria for judgement. *Prevent Med* **16**, 195-210.

Schlesselman, J. (1982). Case-Control Studies: Design, Conduct and Analysis. (Oxford University Press: New York.)

Schmidt, H., Heimann, B., Djukic, M., Mazurek, C., Fels, C., Wallesch, C. W., and Nau, R. (2006). Neuropsychological sequelae of bacterial and viral meningitis. *Brain* **129**, 333-345.

Schmidt, J. A. and Padilla, B. (2003). Self-esteem and family challenge: an investigation of their effects on achievement. *Journal of Youth and Adolescence* **32**, 37-48.

Scholten, R. J., Bijlmer, H. A., Valkenburg, H. A., and Dankert, J. (1994). Patient and strain characteristics in relation to the outcome of meningococcal disease: a multivariate analysis. *Epidemiol.Infect.* **112**, 115-124.

Schubiger, G., Munzinger, J., Dudli, C., and Wipfli, U. (1986). Meningococcal epidemic in a boarding school: a rifampicin-resistant secondary case while under chemoprophylaxis. *Schweiz.Med Wochenschr.* **116**, 1172-1175.

Schuchat, A., Robinson, K., Wenger, J. D., Harrison, L. H., Farley, M., Reingold, A. L., Lefkowitz, L., and Perkins, B. A. (1997). Bacterial meningitis in the United States in 1995. Active Surveillance Team. *N.Engl.J.Med.* **337**, 970-976.

Schwartz, B., Al Tobaiqi, A., Al Ruwais, A., Fontaine, R. E., A'ashi, J., Hightower, A. W., Broome, C. V., and Music, S. I. (1988). Comparative efficacy of ceftriaxone and rifampicin in eradicating pharyngeal carriage of group A Neisseria meningitidis. *Lancet* **1**, 1239-1242.

Schwartz, B., Moore, P. S., and Broome, C. V. (1989). Global epidemiology of meningococcal disease. *Clin.Microbiol.Rev.* **2 Suppl**, S118-S124.

Sclafani, V. Di., Tolou-Shams, M., Price, L. J., and Fein, G. (2002). Neuropsychological performance of individuals dependent on crack-cocaine, or crack-cocaine and alcohol, at 6 weeks and 6 months of abstinence. *Drug and Alcohol Dependence* **66**, 161-171.

Scragg, P., Jones, A., and Fauvel, N. (2001). Psychological problems following ICU treatment. *Anaesthesia* **56**, 9-14.

Segal, S. and Pollard, A. J. (2004). Vaccines against bacterial meningitis. *Br Med Bull* **72**, 65-81.

Seidman, L. J., Biederman, J., Weber, W., Hatch, M., and Faraone, S. V. (1998). Neuropsychological Function in Adults with Attention Deficit Hyperactivity Disorder. *Biol Psychiatry* **44**, 260-268.

Seiffge-Krenke, I. (1995). Stress, coping and relationships in adolescence. (Lawrence Erlbaum Associates.: Mahwah, New Jersey.)

Sell, S., Webb, W., Pate, J., and Doyne, E. (1972). Psychological sequelae to bacterial meningitis: Two controlled studies. *Pediatrics* **4**, 212-217.

Shackley, F., Knox, K., Morris, J. B., Crook, D., Griffiths, D., Mayon-White, R., George, R., Willocks, L., and Moxon, E. (2000). Outcome of invasive pneumococcal disease: a UK based study. Oxford Pneumococcal Surveillance Group. *Arch.Dis.Child* **83**, 231-233.

Shallice, T. (1982). Specific impairments of planning: Philos Trans Roy Soc London Series. *B Biol Sci* **298**, 199-209.

Shapiro, E. D., Aaron, N. H., Wald, E. R., and Chiponis, D. (1986). Risk factors for development of bacterial meningitis among children with occult bacteremia. *J Pediatr.* **109**, 15-19.

Sheps, S. (1993). Sample size and power. *J Invest Surg* **6**, 469-475.

Short, W. R. and Tunkel, A. R. (2000). Changing epidemiology of bacterial meningitis in the United States. *Current Infectious Disease Reports* **2**, 327-331.

Sica, G. T. (2006). Bias in Research Studies. *Radiology* **238**, 780-789.

Sierra, G. V., Campa, H. C., Varcacel, N. M., Garcia, I. L., Izquierdo, P. L., Sotolongo, P. F., Casanueva, G. V., Rico, C. O., Rodriguez, C. R., and Terry, M. H. (1991). Vaccine against group B Neisseria meningitidis: protection trial and mass vaccination results in Cuba. *NIPH Ann* **14**, 195-207.

Silverstein AB (1982). Two- and four-subtest short forms of the Wechsler Adult Intelligence Scale-Revised. *Journal of Clinical and Consulting Psychology* **50**, 415-418.

Simons, G. (2001). Carriage of Neisseria meningitidis among household contacts of patients with meningococcal disease in New Zealand. Eur J Clin Microbiol infect Dis 20[4], 237-242.

Singer, J. J., MacGregor, A. J., Cherkas, L. F., and Spector, T. D. (2006). Genetic influences on cognitive function using The Cambridge Neuropsychological Test Automated Battery. *Intelligence* **34**, 428.

Skirrow, P., Jones, C., Griffiths, R. D., and Kaney, S. (2001). Intensive Care - Easing the trauma. *The Psychologist* **14**, 640-642.

Sleeman, K., Knox, K., George, R., Miller, E., Waight, P., Griffiths, D., Efstratiou, A., Broughton, K., Mayon-White, R. T., Moxon, E. R., and Crook, D. W. (2001). Invasive pneumococcal disease in England & Wales: vaccination implications. *J Infect Dis* **13**, 239-246.

Sleep, T. and Graham, M. (1997). A case of meningococcal endophthalmitis in a well patient. *Br.J Ophthalmol.* **81**, 1016-1017.

Smith, A. G., Fear, N. T., Law, G. R., and Roman, E. (2004). Representativeness of samples from general practice lists in epidemiological studies: case-control study. *BMJ* **328**, 932.

Smith, M. S., Mitchell, J., Corey, L., and et al. (1991). Chronic fatigue in adolescents. *Pediatrics* **88**, 195-202.

Snow, W. G., Tierney, M. C., and Zorzitto, M. L. (1988). One-year test-retest reliability of selected neuropsychological test in older adults. *Journal of Clinical and Experimental Neuropsychology* **10**, (abstract).

Snyder, R. D., Stovring, J., Cushing, A. H., Davis, L. E., and Hardy, T. L. (1981). Cerebral infarction in childhood bacterial meningitis. *J Neurol Neurosurg Psychiatry* **44**, 581-585.

Sorensen, H. T., Nielsen, G. L., Schonheyder, H. C., Steffensen, F. H., Hansen, I., Sabroe, S., Dahlerup, J. F., Hamburger, H., and Olsen, J. (1998). Outcome of pre-hospital antibiotic treatment of meningococcal disease. *J Clin.Epidemiol.* **51**, 717-721.

Soriano-Gabarro, M., Rosenstein, N., and LaForce, F. M. (2004). Evaluation of serogroup A meningococcal vaccines in Africa: a demonstration project. *J Health Popul Nutr* **22**, 275-285.

Sosa, R., Kennell, J., Klaus, M., Robertson, S., and Urrutia, J. (1980). The Effect of a Supportive Companion on Perinatal Problems, Length of Labor, and Mother-infant Interaction. *New England Journal of Medicine* **303**, 597-600.

Sowell, E. R. and Jernigan, T. L. (1998). Further MRI evidence of late brain maturation: limbic volume increases and changing asymmetries during childhood and adolescence. *Developmental Neuropsychology* **14**, 599-617.

Spanjaard, L., Bol, P., de Marie, S., and Zanen, H. C. (1987). Association of meningococcal serogroups with the course of disease in the Netherlands, 1959-83. *Bull.World Health Organ* **65**, 861-868.

Spector, P. E. (1994). Using self-report questionnaires in OB research: A comment on the use of a controversial method. *Journal of Organizational Behavior* **15**, 385-392.

Spencer, P., Erting, C. J., and Marschark, M. (2000). The deaf child in the family and at school. (Lawrence Erlbaum Associates, Publishers, Mahwah, New Jersey.)

Spreen, O. and Strauss, E. (1998). A Compendium of Neuropsychological Tests. (Oxford University Press: New York.)

Sproles, E. T., Azerrad, J., Williamson, C., and Merrill, R. (1969). Meningitis due to Haemophilus influenzae: Long-term sequelae. *Jounral of Pediatrics* **75**, 782-797.

Stanwell-Smith, R. E., Stuart, J. M., Hughes, A O., Robinson, P., Griffin, M. B., and Cartwright, K. (1994). Smoking, the environment and meningococcal disease: a case-control study. *Epidemiol Infect* **112**, 315-328.

Staquet, M. J., Hays, R. D., and Fayers, P. M. (1998). Quality of life assessment in clinical trials: methods and practice. (Oxford University Press: Oxford.)

Starfield, B. (1995). The adolescent child health and illness profile: a population-based measure of health. *Medical care* **33**, 553-566.

Steer, R. A., Ball, R., Ranieri, W. F., and Beck, A. T. (1997). Further evidence for the construct validity of the Beck Depression Inventory-II with psychiatric outpatients. *Psychological Reports* **80**, 443-446.

Steer, R. A. and Clark, D. A. (1997). Psychometric characteristics of the Beck Depression Inventory-II with college students. *Measurement and Evaluation in Counseling and Development* **30**, 128-136.

Steer, R. A., Kumar, G., Ranieri, W. F., and Beck, A. T. (1998). Use of the Beck Depression Inventory—II with adolescent psychiatric outpatients. *Journal of Psychopathology and Behavioral Assessment* **20**, 127-137.

Stephens, D. S. (1999). Uncloaking the meningococcus: dynamics of carriage and disease. *Lancet* **353**, 941-942.

Stephens, D. S. (2007a). Conquering the Meningococcus. *Microbiol Rev* **31**, 3-14.

Stephens, D. S., Greenwood, B., and Brandtzaeg, P. (2007b). Epidemic meningitis, meningococcaemia, and Neisseria meningitidis. *Lancet* **369**, 2196-2210.

Stephens, D. S., Hajjeh, R. A., Baughman, W. S., Harvey, R. C., Wenger, J. D., and Farley, M. M. (1995). Sporadic meningococcal disease in adults: results of a 5-year population-based study. *Ann.Intern.Med.* **123**, 937-940.

Stephenson, T. (1998). Clinical management of meningococcal disease. Coning may occur without lumbar puncture being done. *BMJ* **316**, 1015.

Stern, M., Norman, S., and Zevon, M. (1993). Adolescents with cancer: Self-image and perceived social support as indexes of adaptation. .*Journal of Adolescent Research,* **B(1)**, 124-142.

Stern, Y. (2003). The Concept of Cognitive Reserve: A Catalyst for Research. *Journal of Clinical and Experimental Neuropsychology* **25**, 589-593.

Stern, Y., Zarahn, E., Hilton, H. J., Flynn, J., DeLaPaz, R., and Rakitin, B. (2003). Exploring the neural basis of cognitive reserve. *J Clin Exp Neuropsychol.* **25**, 691-701.

Sterne, J. A. and Davey, Smith G. (2001). Sifting the evidence-what's wrong with significance tests? *BMJ* **322**, 226-231.

Stiehm, E. R. and Damrosch, D. S. (1966). Factors in the prognosis of meningococcal infection. Review of 63 cases with emphasis on recognition and management of the severely ill patient. *J Pediatr.* **68**, 457-467.

Stollenwerk, N., Maiden, M. C., and Jansen, V. A. (2004). Diversity in pathogenicity can cause outbreaks of meningococcal disease. *Proc. Natl. Acad Sci U.S.A* **101**, 10229-10234.

Stovall, S. H. and Schutze, G. E. (2002). Meningococcal infections in children from Arkansas. *Pediatr.Infect.Dis.J.* **21**, 366-370.

Strang, J. R. and Pugh, E. J. (1992). Meningococcal infections: reducing the case fatality rate by giving penicillin before admission to hospital. *BMJ* **305**, 141-143.

Straus, S. E., Tosato, G., Armstrong, G., and Lawley, T. (1985). Persisting illness and fatigue in adults with evidence of Epstein-Barr infection. *Ann Intern Med* **102**, 7-16.

Stuart, J. M., Cartwright, K. A., Robinson, P. M., and Noah, N. D. (1989). Effect of smoking on meningococcal carriage. *Lancet* **2**, 723-725.

Stuart, J. M., Cartwright, K. A. V., Dawson, J. A., Rickard, J., and Noah, N. D. (1988). Risk factors for meningococcal disease: a case-control study in south west England. *Community Med* **2**, 139-145.

Stuber, M. L. and Shemesh, E. (2006). Post-traumatic Stress Response to Life-Threatening Illnesses in Children and Their Parents (article in press). *Child Adolesc Psychiatric Clin N Am.*

Sturms, L. M., van der Sluis, C. K., Stewart, R. E., Groothoff, J. W., ten Duis, H. J., and Eisma, W. H. (2005). A prospective study on paediatric traffic injuries: health-related quality of life and post-traumatic stress. *Clin Rehabil* **19**, 312-322.

Sullivan, E. V., Farma, R., Rosenbloom, M. J., and Pfefferbaum, A. (2002). A Profile of Neuropsychological Deficits in Alcoholic Women. *Neuropsychology* **16**, 74-83.

Sullivan, T. D. and LaScolea, L. J., Jr. (1987). Neisseria meningitidis bacteremia in children: quantitation of bacteremia and spontaneous clinical recovery without antibiotic therapy. *Pediatrics* **80**, 63-67.

Sutton, K., Cooper, M., Pimm, J., and Wallace, L. (1999). Anxiety in Chronic Obstructive Pulmonary Disease: The Role of Illness Specific Catastrophic Thoughts. *Cognitive Therapy and Research* **23**, 573-585.

Swartley, J. S., Marfin, A. A., Edupuganti, S., Liu, L. J., Cieslak, P., Perkins, B., Wenger, J. D., and Stephens, D. S. (1997). Capsule switching of Neisseria meningitidis. *Proc.Natl.Acad.Sci.U.S.A* **94**, 271-276.

Sweeney, J. A., Kmiec, J. A., and Kupfer, D. J. (2000). Neuropsychologic Impairments in Bipolar and Unipolar Mood Disorders on the CANTAB Neurocognitive Battery. *Biol Pyschiatry* **48**, 674-685.

Swets, J. A. (1964). Signal detection and recognition by human observers. (Wiley: New York.)

Szklo, M. (1998). Population-based Cohort Studies. *Epidemiol Rev* **20**, 81-90.

Szklo, M. and Nieto, F. J. (2000). Understanding lack of validity: bias. In 'Epidemiology: beyond the basics.'. (Ed. Gaithersburg.) pp. 125-176. Aspen.)

Takakura, M. (1997). Relationship between Body Type, Subjective Symptoms and Health Awareness in Junior High School Students. *Jpn J Public Health* **44**, 131-138.

Tapert, S. A. and Brown, S. A. (1999). Neuropsychological correlates of adolescent substance abuse: four-year outcomes. *Journal of the International Neuropsychological Society* **5**, 481-493.

Tappero, J. W., Reporter, R., Wenger, J. D., Ward, B. A., Reeves, M. W., Missbach, T. S., Plikaytis, B. D., Mascola, L., and Schuchat, A. (1996). Meningococcal disease in Los Angeles County, California, and among men in the county jails. *N.Engl.J.Med.* **335**, 833-840.

Taylor, E. M. (1959). The appraisal of children with cerebral deficits. (University Press: Cambridge MA.)

Taylor, G. H., Michaels, R., Mazur, P., Bauer, R., and Liden, C. (1984). Intellectual, neuropsychological, and achievement outcomes in children 6 to 8 years after recovery from Haemophilus influenzae meningitis. *Pediatrics* **74**, 198-205.

Taylor, G. H., Schatschneider, C., Watters, G. V., Mills, E. L., Gold, R., MacDonald, N., and Michaels, R. H. (1996). Acute-Phase Neurological Complications of Haemophilus Influenzae Type b Meningitis: Association with developmental problems at school age. *Journal of Child Neurology* **13**, 113-119.

Taylor, R. (1999). National Adult Reading Test performance in established dementia. *Archives of Gerontology and Geriatrics* **29**, 291-296.

Taylor, R. R., Jason, L. A., and Curie, C. J. (2002). Prognosis of Chronic Fatigue in a Community-Based Sample. *Psychosomatic Medicine* **64**, 319-327.

Taylor, S. E., Cousino Klein, L., Lewis, B. P., and Gruenewald, T. (2000). Biobehavioural responses to stress in females: tend-and-befriend, not fight-or-flight. *Psychological Review* **30**, 965-974.

Tejani, A., Dobias, B., and Sambursky, J. (1982). Long-term prognosis after *H. influenzae* meningitis: prospective evaluation. *Dev Med Child Neurol* **24**, 338-343.

Teri, L. (1982). The use of the Beck Depression Inventory with adolescents. *J. Abnorm. Child .Psychol.* **10**, 277-284.

The Meningococcal Disease Surveillance Group (1974). Meningococcal disease secondary attack rate and chemoprophylaxis in the United States. *JAMA* **235**, 261-265.

Thomas, J. C., Bendana, N. S., Waterman, S. H., Rathburn, M., Arakere, G., Frasch, C. E., Wenger, J. D., Magsombol, V., and Clark, J. H. (1991). Risk Factors for Carriage of Meningococcus in the Los Angeles County Men's Jail System. *American Journal of Epidemiology* **133**, 286-295.

Thompson, M. J., Ninis, N., Perera, R., Mayon-White, R., Phillips, C., Bailey, L., Harnden, A., Mant, D., and Levin, M. (2006). Clinical recognition of meningococcal disease in children and adolescents. *Lancet* **367**, 397-403.

Thomson, A. P., Sills, J. A., and Hart, C. A. (1991). Validation of the Glasgow Meningococcal Septicemia Prognostic Score: a 10-year retrospective survey. *Crit Care Med* **19**, 26-30.

Thomson, A. P. J. and Riordan, F. A. I. (2000). The management of meningococcal disease. *Current Paediatrics* **10**, 104-109.

Tikhomirov, E., Santamaria, M., and Esteves, K. (1997). Meningococcal disease: public health burden and control. *World Health Stat Q* **50**, 170-177.

Torres, I. J., Flashman, L. A., O'Leary, D. S., and Andreasen, N. C. (2001). Effects of retroactive and proactive interference on word list recall in schizophrenia. *J Int.Neuropsychol.Soc.* **7**, 481-490.

Torres, I. J., O'Leary, D. S., and Andreasen, N. C. (2004). Symptoms and interference from memory in schizophrenia: evaluation of Frith's model of willed action. *Schizophrenia Research* **69**, 35-43.

Travis, F., Teece, J., Arenander, A., and Wallace, K. (2002). Patterns of EEG coherence, power, and contingent negative variation characterize the integration of transcendental and waking states. *Biological Psychology* **61**, 293-319.

Trotter, C. L., Andrews, N. J., Kaczmarski, E. B., Miller, E., and Ramsay, M. E. (2004). Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. *Lancet* **364**, 365-367.

Trotter, C. L., Gay, N. J., and Edmunds, W. J. (2005). Dynamic models of meningococcal carriage, disease, and the impact of serogroup C conjugate vaccination. *Am J Epidemiol* **162**, 89-100.

Trotter, C. L., Ramsay, M. E., and Kaczmarski, E. B. (2002). Meningococcal serogroup C conjugate vaccination in England and Wales: coverage and initial impact of the campaign. *Communicable Disease and Public Health* **5**, 220-225.

Tudor-Williams, G., Frankland, J., Isaacs, D., and et al. (1989). *Haemophilus influenzae* type b disease in the Oxford region. *Arch Dis Child* **64**, 517-519.

Tulloch, A. L., Blizzard, L., and Pinkus, Z. (1997). Adolescent-parent communication in self-harm. *Journal of Adolescent Health* **21**, 267-275.

Tully, J., Viner, R. M., Coen, P. G., Stuart, J. M., Zambon, M., Peckham, C., Booth, C., Klein, N., Kaczmarski, E., and Booy, R. (2006). Risk and protective factors for meningococcal disease in adolescents: matched cohort study. *BMJ* **332**, 445-450.

Tunkel, A. R. and Dolin, R. (2000). Acute meningitis. In 'Principles and Practice of Infectious Disease'. (G. I. Mandel, J. E. Bennett, and R. DolinEds.) pp. 959-997. (Churchill Livingstone: Philadelphia, PA.)

Usen, S., Adegbola, R., and Mullholland, K. (1998). Epidemiology of invasive pneumococcal disease in the Western Region, The Gambia. *Pediatr Infect Dis J* **17**, 23-28.

Ustun, T. B. (2000). Cross-national epidemiology of depression and gender. *Journal of Gender Specific Medicine* **3**, 54-58.

van De Beek D., Schmand, B., de Gans, J., Weisfelt, M., Vaessen, H., Dankert, J., and Vermeulen, M. (2002). Cognitive impairment in adults with good recovery after bacterial meningitis. *J Infect Dis* **186**, 1047-1052.

van de Putte, E. M., Engelbert, R. H., Kuis, W., Sinnema, G., Kimpen, J., and Uiterwaal, C. (2005). Chronic fatigue syndrome and health control in adolescents and parents. *Arch Dis Child.* **90**, 1020-1024.

van Deuren, M., Brandtzaeg, P., and van der Meer, J. W. (2000). Update on meningococcal disease with emphasis on pathogenesis and clinical management. *Clin.Microbiol.Rev.* **13**, 144-66, table.

van Deuren, M., van, der, V, Bartelink, A. K., van Dalen, R., Sauerwein, R. W., and van der Meer, J. W. (1995). Correlation between proinflammatory cytokines and anti-inflammatory mediators and the severity of disease in meningococcal infections. *J Infect.Dis.* **172**, 433-439.

Van Ommeren, M. (2003). Validity issues in transcultural epidemiology. *The British Journal of Psychiatry* **182**, 378.

Vargha-Khadem, F. (1985). Development of intelligence and memory in children with hemiplegic cerebral palsy. *Brain* **108**, 677-696.

Vaux, A. (1985). Variations in social support associated with gender, ethnicity, and age. *Journal of Social Issues* **41**, 89-110.

Veale, D. M., Sahakian, B. J., Owen, A. M., and Marks, I. M. (1996). Specific cognitive deficits in tests sensitive to frontal lobe dysfunction in obsessive-compulsive disorder. *Psychological Medicine* **26**, 1261-1269.

Veiel, H. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology* **19**, 587-603.

Verheul, A. F., Snippe, H., and Poolman, J. T. (1993). Meningococcal lipopolysaccharides: virulence factor and potential vaccine component. *Microbiol. Rev.* **57**, 34-49.

Vieusseux, M. (1806). Memoire sur la maladie qui a regne a Geneve au printemps de 1805. *J Med Chir Pharmacol* **11**, 163-182.

Viner, R. M. and Barker, M. (2005). Young people's health: the need for action. *BMJ* **330**, 901-903.

Vogel, U. and Frosch, M. (1999). Mechanisms of neisserial serum resistance. *Mol. Microbiol.* **32**, 1133-1139.

Volker, T. (1995). The clinical report: Integrating family assessment instruments into family. *Counseling & Therapy for Couples & Families* **3**, 284-297.

Wacholder, A., McLaughlin, J. K., Silverman, D. T., and Mandel, J. S. (1992a). Selection of controls in case-control studies. I. Principles. *American Journal of Epidemiology* **135**, 1019-1028.

Wacholder, S, Silverman, DT, McLaughlin, JK, and Mandel, JS (1992b). Selection of controls in case-control studies. III. Design options. *Am J Epidemiol.* **135**, 1042-1050.

Wacholder, S., Silverman, D. T., McLaughlin, J. K., and Mandel, J. S. (1992c). Selection of controls in case-control studies: II Type of controls. *American Journal of Epidemiology* **135**, 1029-1041.

Wallace, M., Harcourt, D., and Rumsey, N. (2007). Adjustment to appearance changes resulting from meningococcal septicaemia during adolescence: A qualitative study. *Developmental Neurorehabilitation* **10**, 125-132.

Wallman, K. E., Morton, A. R., Goodman, C., Grove, R., and Guilfoyle, M. (2004). Randomized controlled trial of graded exercise in chronic fatigue syndrome. *MJA* **180**, 444-448.

Walsh, K. W. (1985). Understanding brain damage. (Churchill-Livingstone: Edinburgh.)

Wang, J. F., Caugant, D. A., Li, X., and et al (1992). Clonal and antigenic analysis of serogroup A Neisseria meningitidis with particular reference to epidemiological features of epidemic meningitis in the People's Republic of China. *Infect immun* **60**, 5282.

Wang, V. J., Kuppermann, N., Malley, R., Barnett, E. D., Meissner, H. C., Schmidt, E. V., and Fleisher, G. R. (2001). Meningococcal disease among children who live in a large metropolitan area, 1981-1996. *Clin.Infect.Dis.* **32**, 1004-1009.

Ware, J E and Sherbourne, C (1992). Short-Form Health Survey 1: conceptual framework and item selection. *Med Care* **30**, 473-483.

Ware, J E., Kosinski, M, and Bayliss, M S et al. Comparison of methods for scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical outcomes Study. Med Care 33, AS264-79. 1995.

Ware, J. E., Kosinski, M., and Gandek, B. SF-36 Physical and Mental Health Summary Scales: A User's Manual. 1994. Boston, The Health Institute, New England Medical Center.

Ware, J. E., Snow, K. K., Kosinski, M., and Gandek, B. SF36 Health Survey: Manual and Interpretation Guide. 1993. Boston, MA, The Health Institute, New England Medical Center.

Watson, J. M., Nicholas, S., and James, P. (1996). Meningococcal infection and influenza: do surveillance data support as association? In 'Options for the control of influenza III'. pp. 82-84. (Elsevier Science: Amsterdam.)

Watt, K. J. and O'Carroll, R. E. (1999). Evaluating methods for estimating premorbid intellectual ability in closed head injury. *J Neurol Neurosurg Psychiatry* **66**, 474-479.

Wechsler, D. (1981). Manual for the Wechsler Adult Intelligence Scale-Revised. (Psychological Corporation: San Antonio, TX.)

Weichselbaum, A. (1887). Uerber die Aetiologie der akuten Meningitis cerebro-spinalis. *Fortschr Med* **5**, 573-583.

Weissman, M. M., Wolk, S., and Goldstein, R. B. (1999). Depressed adolescents grown up. *Journal of the American Medical Association* **281**, 1701-1713.

Weitzman, M. (1986). School absence rates as outcome measures in studies of children with chronic illness. *J Chron Dis* **39**, 799-808.

Wells, M. and Gibbons, R. B. (1997). Primary meningococcal arthritis: case report and review of the literature. *Mil.Med* **162**, 769-772.

Wessely, S. and Powell, R. (1998). Fatigue syndromes: a comparison of chronic 'post-viral' fatigue with neuromuscular and affective disorders. *J Neurol Neurosurg Psychiatry* **52**, 940-948.

Whisman, M. A., Perez, J. E., and Ramel, W. (2000). Factor structure of the Beck Depression Inventory-Second Edition (BDI-II) in a student sample. *J Clin Psychol* **56**, 545-551.

White, P. D., Thomas, J. M., and Amess et al. (1998). Incidence, risk and prognosis of acute and chronic fatigue syndromes and psychiatric disorders after glandular fever. *Br J Psychiatry* **173**, 475-481.

WHO. Bacterial Infections: Vaccine Research Report. 2005. WHO.

Wigley, F. and Flavahan, N. (1996). RAYNAUD'S PHENOMENON. *Rheumatic Disease Clinics of North America* **22**, 765-781.

Willis, T. (1684). A description of epidemical feaver. In 'Practice of Physics, Treatise VIII'. (Ed. T. Dring.) pp. 46-54. London.)

Wills, T. A. and Cleary, S. D. (1996). How are social support effects mediated? A test with parental support and adolescent substance use. *Journal of Personality and Social Psychology* **71**, 937-952.

Willshire, D., Kinsella, G., and Prior, M. (1991). Estimating WAIS-R IQ from the National Adult Reading Test (NART): A cross-validation. *Journal of Clinical and Experimental Neuropsychology* **13**, 204-217.

Wilson, G. A., Pritchard, M. E., and Revalee, B. (2005). Individual differences in adolescent health symptoms: the effects of gender and coping. *J Adolesc* **28**, 369-379.

Wilson, R. S., Gilley, D. W., Bennett, D. A., Beckett, L. A., and Evans, D. A. (2000). Hallucinations, delusions, and cognitive decline in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **69**, 172-177.

Wolbeek, M., van Doornen, L. J., Kavelaars, A., and Heijen, C. (2006). Severe Fatigue in Adolescents: A common phenomenon? *Pediatrics* **117**, 1078-1086.

World Health Organisation. Control of epidemic meningococcal disease: practical guidelines. (2nd Ed.). 2002a. World Health Organisation.

World Health Organisation. (1999). Bacterial etiology of serious infections in young infants in developing countries: results of a multicenter study. The WHO Young Infants Study Group. *Pediatr Infect Dis J* **18 (suppl 10)**, S17-22.

World Health Organization. Emergence of W135 meningococcal disease. Report of a WHO consultation, 17-18 September 2001. 2002b. Geneva, World Health Organization.

Wylie, P. A., Stevens, D., Drake, W., III, Stuart, J., and Cartwright, K. (1997). Epidemiology and clinical management of meningococcal disease in west Gloucestershire: retrospective, population based study. *BMJ* **315**, 774-779.
Yazdankhah, S. P. and Caugant, D. A. (2004). Neisseria meningitidis: an overview of the carriage state. *J Med Microbiol.* **53**, 821-832.

Young, L. S., LaForce, F. M., Head, J. J., Freeley, J. C., and Bennett, J. V. (1972). A simultaneous outbreak of meningococcal and influenza infections. *N Engl J Med* **27**, 5-9.

Yule, W., Bolton, D., Udwin, O., Boyle, S., O'Ryan, D., and Nurrish, J. (2000). The long-term psychological effects of a disaster experienced in adolescence I: The incidence and course of PTSD. *J Child Psychol Psychiatry* **41**, 503-511.

Zollinger, W. D., Boslego, J., Moran, E., Garcia, J., Cruz, C., Ruiz, S., Brandt, B., Martinez, M., Arthur, J., Underwood, P., and . (1991). Meningococcal serogroup B vaccine protection trial and follow-up studies in Chile. The Chilean National Committee for Meningococcal Disease. *NIPH Ann.* **14**, 211-212.

APPENDIX A – PUBLICATIONS AND PRESENTATIONS

Publications

Borg, J., Christie, D., Coen, P., Booy, R., Viner, R. 2005. The Impact of meningococcal disease in adolescence: Longitudinal prospective population-based case-control study. *Journal of Adolescent Health*, vol. 36, no. 2, pp. 106-107.

Borg, J., Christie, D., Coen, P., Booy, R., Viner, R. 2003. Outcomes of meningococcal disease during the teenage peak, *Arch Dis Child*, 88 (Suppl I): A1-A7.

Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: a prospective matched cohort study. *Pediatrics*, In Press, 2008.

Presentations

- The Middlesex Hospital, London, Department of Adolescence, 2002
- St Pancras Hospital, Camden & Islington Mental Health Service, 2003
- British Psychological Society, Annual conference, Staffordshire University, 2004
- Royal College of Paediatrics and Child Health (RCPCH), University of York – Plenary session, 2004
- Great Ormond Street Hospital, Department of Psychological Medicine, 2005
- Royal Free Hospital, Department of Child Health, 2005
- Meningitis Research Foundation, Conference, – '*Meningitis and Septicaemia in Children and Adults*'. 2005
- University College London Hospitals – Grand Rounds, 2006